TO STUDY THE PREVALENCE OF ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS

Dissertation submitted in partial fulfillment of regulation for the award of M.D. Degree in General Medicine (Branch I)

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CERTIFICATE

Certified that this is the bonafide dissertation done by ***DR SUJA P SUKUMAR*** *and submitted in partial fulfillment of the requirements for the Degree of M.D., General Medicine, Branch I of The Tamilnadu Dr. M.G.R. Medical University, Chennai.*

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I solemnly declare that the dissertation titled **"TO STUDY THE PREVALENCE OF ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS"** was done by me from September 2009 to September 2010 under the guidance and supervision of **Professor Dr. NEDUMARAN, MD, DM.**

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Introduction

INTRODUCTION

Diabetes mellitus is the commonest endocrine disease affecting mankind. The incidence of this disease continues to be on the rise all over the world. The magnitude of problem is further compounded by various catastrophic macro and microvascular complications targeting the vital organs in the body.

Coronary artery disease (CAD) is the leading cause of death in patients with type 2 diabetes and is often asymptomatic because of silent myocardial ischaemia. The high mortality rate is partly due to the diabetic state per se, above and beyond the clustering of other risk factors such as hypertension, dyslipidemia, and obesity. The prevalence of CAD in our country earlier varied from 15 – 65/1000 population, but now it has increased to about 80 – 120/1000, making it a major cause of morbidity and mortality.[1]

Coronary artery disease is multifactorial in etiology and has several important risk factors, out of which diabetes is one of the important modifiable risk factor. Data from Framingham heart study demonstrate the increased and poor prognosis of cardiac disease in diabetes. Mortality related to cardiovascular disease is doubled in diabetic men and quadrupled in diabetic women over that in their non diabetic counterparts.[2] Diabetes is considered a ‘coronary artery disease (CAD)

equivalent' because patients with diabetes without known CAD have a similar cardiac event rate to patients without diabetes who had a prior myocardial infarction (MI).[2]

CAD is the leading cause of morbidity and mortality in diabetic patients and frequently manifests itself silently and prematurely. Thus a classical cardiovascular risk factor is 'HYPERGLYCEMIA'. Clinical evidence demonstrates that the hyperglycemia in diabetes correlates well with risk and severity of microvascular and macrovascular complications and improving hyperglycemia reduces this risk. CAD can be asymptomatic in diabetes and may present with sudden death, myocardial infarction, arrhythmia, silent myocardial ischemia or heart failure. The association between diabetes and asymptomatic CAD has been attributed to an autonomic neuropathy.[3] Early detection of asymptomatic CAD in type 2 diabetes may prevent catastrophic cardiac events. However, periodical thorough clinical examination and resting E.C.G. may fail to detect coronary artery disease. Hence sophisticated cardio vascular non invasive tests should then be proposed for early detection of CAD in these patients. Exercise electrocardiograph can identify the majority of patients likely to have significant ischaemia during their daily activities and remains the most important screening test for significant CAD.[3] This study was designed to evaluate asymptomatic coronary artery disease in selected diabetic patients by exercise treadmill test. [2]

Aims & Objectives

AIM AND OBJECTIVES

1. To study the prevalence of asymptomatic coronary artery disease in type 2 diabetes mellitus patients.

2. To study the relation of asymptomatic coronary artery disease with duration of diabetes mellitus

Review of Literature

REVIEW OF LITERATURE

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia. Several distinct types of diabetes mellitus exist and are caused by a complex interaction of genetic, environmental factors, and life style choices. Depending on the etiology of diabetes mellitus, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems. Some forms of diabetes mellitus are characterized in terms of their specific etiology or pathogenesis, but the underlying etiology of the most common forms remains unclear. Persons developing the disease can be categorized according to clinical stages and other characteristics even in the absence of knowledge of the etiology.

HISTORICAL ASPECTS

"Diabetes is…a melting down of the flesh and limbs into urine…the flow is incessant, as if from the opening of aqueducts…The melting is rapid, the death speedy. Moreover, life is disgusting and painful." – ***Arataeus Turkish physician from the second century AD.***

The knowledge of Diabetes mellitus dates back to centuries before Christ. The Egyptian Papyrus Ebers in 1500 BC described an illness associated with passage of "much urine". Greek physician **Arateaus** of **Coppadocia** (200 AD) gave the word 'diabetes' meaning 'running through a siphon'. Indians knew about the disease before Arateaus. An interesting amount of information is available from **Charaka Samhita** & **Sushrutha Samhita** compiled about 300 BC and 400 BC respectively. It was John Rollo (1809) who was one of the first to use adjunctive "mellitus" (mellitus: honey) to distinguish from other polyuric states in which urine was tasteless (Greek: insipidus). The 16th to 18th centuries have been termed the 'DIAGNOSTIC' period, as diabetes mellitus was then identified as a separate disease entity, while the mid to late 19th century may be regarded as the first 'EXPERIMENTAL' period, during which the glucoregulatory role of the pancreas became clear and the biochemical disturbances of diabetes were initially characterized.[5] Finally, the 20th century has seen a dramatic increase in knowledge about diabetes. The discovery of insulin in 1921-22 has had profound scientific, clinical and social consequences.[6]

CLASSIFICATION OF DIABETES AND OTHER CATEGORIES OF GLUCOSE REGULATION

Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy.[8]

Etiologic classification of diabetes mellitus

I. Type 1 Diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

A) Immune-mediated B) Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes

A. Genetic defects of β-cell function characterized by mutations in :

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
2. Glucokinase (MODY 2)
3. HNF – 1α (MODY 3)
4. Insulin promoter factor (IPF) 1 (MODY 4)
5. HNF – 1β (MODY 5)
6. Neuro D1 (MODY 6)

7. Mitochondrial DNA
8. Proinsulin or insulin conversion

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes.

C. Diseases of the exocrine pancreas – pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy.

D. Endocrinopathies – acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug or chemical induced – Vacor, pentamidine, nicotinic acid,glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, phenytoin, α– interferon, protease inhibitors, clozapine, betablockers.

F. Infections – congenital rubella, cytomegalovirus, coxsackie.

G. Uncommon forms of immune-mediated diabetes – "stiff-man" syndrome, anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes – Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome.

IV. Gestational diabetes mellitus (GDM)

EPIDEMIOLOGY AND BURDEN OF TYPE-2 DM

Diabetes mellitus is an "Iceberg" disease. According to recent estimates the prevalence of Diabetes mellitus in adults is around 6.4% worldwide. It is projected that the disease prevalence will be 7.8% by the year 2030, with global diabetic population reaching 438 million. Of this, close to 77% of the global burden of disease is projected to occur in developing countries. Type 2 DM forms 95% of all diabetes, an estimated 30 million persons in the South-East Asian region are affected at present and it is estimated that by the year 2025 there will be nearly 80 million diabetics in this region, the highest among all WHO regions. Among this the greatest increase will be in India i.e. from 19.4 million (1995) to 57.2 million by 2025. The prevalence of diabetics in Indian adults was found to be 2.4% in rural and 4-11.6% in urban dwellers.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS
• Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a] or • Fasting plasma glucose ≥ 7.0 mol/L (126 mg/dL)[b] or • Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test [c]

a) Random is defined as without regard to time since the last meal.

b) Fasting is defined as no caloric intake for atleast 8 h.

c) The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

(source: Adapted from ADA,2004)

The use of the hemoglobin A1C (HbA1C) for the diagnosis of diabetes is not recommended at this time.

SCREENING FOR DIABETES

Diabetes is frequently not diagnosed until complications appear and approximately one third of all people with diabetes may be undiagnosed. However, there are no randomized trials demonstrating benefits of early diagnosis through screening of asymptomatic individuals. But wide spread use of FPG as a screening test for Type 2 diabetes mellitus is justified in individuals at high risk.

TYPE 2 DIABETES MELLITUS

This form of Diabetes mellitus was previously referred to as non-insulin dependent Diabetes mellitus or adult onset diabetes. It is a term used for individuals who have insulin resistance and usually have relative insulin deficiency. Atleast initially and often throughout their life time, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes, and it is likely that the proportion of patients in this category will decrease in the future as identification of specific pathogenic processes and genetic defects permits better differentiation among them and a more definitive subclassification.Many patients with this form of Diabetes mellitus are obese and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis seldom occurs in this type of diabetes, it usually arises in association with the stress of another illness such as infection. This form of Diabetes mellitus frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. The risk of developing this form of Diabetes mellitus increases with age, obesity and lack of

physical activity. It occurs more frequently in women with prior Gestational Diabetes Mellitus (GDM) and in individuals with hypertension or dyslipidemia and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition; more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of Diabetes mellitus are complex and not clearly defined.

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus is characterized by excessive increase in plasma glucose levels which results from failure in inhibition of hepatic glucose production in combination with reduction in uptake by tissues especially muscles. These abnormalities result from combination of inadequate insulin secretion and insulin resistance by both liver and muscle failure to suppress plasma glucose.

Complications of Diabetes[8]

1. Acute complications

a) Metabolic: Diabetic ketoacidosis, hyper osmolar non-ketotic coma, lactic acidosis and hypoglycemia.

b) Non metabolic: myocardial infarction, cerebrovascular stroke, overwhelming sepsis and infection.

2. Chronic complications

Microvascular	Macrovascular
Retinopathy	Coronary artery disease (CAD/CHD)
Nephropathy	Cerebrovascular disease (CVD)
Neuropathy	Atherosclerotic arterial obstruction
Diabetic foot ulcer	

Others

- Infections: UTI,Tuberculosis, Candidiasis – oral / volvovaginal, Mucor mycosis, Necrotising fasciitis, Periodontitis
- Duputrens contracture
- Pseudogout

Diabetic Neuropathy

Diabetic neuropahy occurs in approximately 50% of individuals with long standing type 1 or type 2 diabetes mellitus. As with other complications of diabetes mellitus, the development of neuropathy correlates with the duration of diabetes and glycemic control.

Classification

Symmetric	Asymmetric
Distal sensory polyneuropathy Autonomic neuropathy Chronic proximal motor neuropathy	Acute or subacute proximal motor neuropathy Cranial mononeuropathy Truncal neuropathy Entrapment neuropathies

DIABETIC RETINOPATHY

Diabetic retinopathy is the most frequent cause of blindness among adults aged 20-74 years. During the first two decades of disease, nearly all patients with type 1 diabetes mellitus and >60% with type 2 diabetes mellitus have retinopathy.

In type 2 diabetes mellitus, 21% of patients have retinopathy at first diagnosis.

Classification [10]

Non Proliferative Diabetic Retinopathy (NPDR)

Proliferative Diabetic Retinopathy

Advanced PDR

Diabetic Nephropathy

Diabetes has become the most common single cause of endstage renal disease (ESRD) world wide. About 20-30% of patients with type 1 or type 2 diabetes mellitus develop evidence of nephropathy, but in type 2 diabetes a considerably smaller fraction of these progress to ESRD. However, because of much higher prevalence of type 2 diabetes mellitus, these patients constitute over half of patients with nephropathy needing dialysis.[4]

CATEGORY	Spot collection (µg/mg creatinine)	24 Hr collection (mg/24 hrs)	Timed collection (µg/min)
Normal	<30	<30	<20
Microalbuminuria	30 – 299	30-299	20-199
Clinical albuminuria	≥300	≥300	≥200

The diabetic nephropathy progresses from appearance of low but abnormal levels of (≥ 30mg to 299 mg/day or 20µg/min) albumin in urine (stage of microalbuminuria) to stage of macroalbuminuria / clinical albuminuria (≥300mg/dl or ≥200µg/min) to ESRD. Progress from microalbuminuria to macroalbuminuria usually takes 10-15 years. ESRD develops in 50% of type 1 diabetic individuals with clinical nephropathy

within 10 years and in 75% by 20 years. But in type 2 DM, even after 20 years of overt nephropathy only 20% progress to ESRD.

Screening for Microalbuminuria

A test for the presence of urinary microalbumin should be performed at diagnosis in patients with type 2 diabetes mellitus and after 5 years of disease duration in those with type 1 diabetes mellitus, then repeated annually.

DIABETES MELLITUS AND CORONARY ARTERY DISEASE

With better control of metabolic and infective complications, diabetes has predominantly become a disease of the cardiovascular system. Cardio-Diabetology is emerging as a subspeciality throughout the globe to tackle the menace of cardiac related mortality in diabetes, particularly Type 2 DM. Diabetes mellitus has a greater prevalence of coronary artery disease, cardiomyopathy and congestive cardiac failure[12,13.]Diabetes not only involves the epicardial coronary arteries but also the intramural coronary arteries. Silent ischemic events constitute a special feature of presentation.CAD in DM patients is not only frequent but also occurs at younger age and the involvement is more extensive.

The Framingham study has shown that cardiovascular mortality is twice in diabetic men and four times in diabetic women as compared with nondiabetic counter parts. Prevalence of angina pectoris is 60% greater in

diabetic men and 90% greater in diabetic women than in a nondiabetics. Incidence of left main coronary artery is higher (13%) in diabetic versus non diabetic (60%), sudden death occurs 50% more in diabetic men and 30% more in diabetic women. Prevalence of silent myocardial infarction and silent myocardial ischaemia is more in diabetics. In diabetes mellitus, there is greater prevalence of painless sudden death particularly during sleep. Silent myocardial ischaemia is evidenced during treadmill and thallium stress tests. Incidence of painless ST depression is twice in diabetics (75%) versus non diabetics (35%)

In a study,16 of 30 asymptomatic diabetics with peripheral neuropathy, as determined by nerve function studies and compared them with 30 asymptomatic diabetics without evidence of neuropathy. All patients underwent exercise ECG and they found that 23.33% of all had abnormal responses**.** However, the two groups did not differ in prevalence of silent myocardial ischemia.

Another study,[17] evaluated the prevalence and characteristics of silent myocardial ischemia in 50 asymptomatic, non insulin dependent diabetes mellitus patients with normal resting electrocardiogram on 48 hours holter monitoring.They found that prevalence of silent myocardial ischemia during daily activities in asymptomatic diabetic patients was very high (58%). Further, silent myocardial ischemia was related to the

presence of other risk factors for coronary artery disease and to diabetic complications like retionopathy, neuropathy and nephropathy. However, silent myocardial ischemia was not related to cardiac autonomic neuropathy.

In another study[18] of 136 asymptomatic diabetics and 80 asymptomatic controls with exercise ECG, 24 hour holter, Thallium Scintigraphy and coronary angiography. 29% diabetics and 5% controls were positive in one or more noninvasive test., 12/34 diabetic who underwent angiography had significant stenosis and 7 had unimportant stenosis, whereas only one control had unimportant stenosis. 30 diabetics with known or suspected CAD with exercise ECG and autonomic function test, they found that 60% had painless ST segment changes of those with severe autonomic neuropathy, 92% had no pain, whereas those with mild autonomic dysfunction or normal autonomic functions had 39% prevalence of silent myocardial ischemia

One study[21] evaluated the significance of ischemic ST depression without anginal chest pain during exercise testing among patients with diabetes mellitus, using the data on 45 such patients from the Coronary Artery Surgery study registry. These patients (group 1 silent ischemia) were compared with 37 diabetic patients with both ischemic ST depression and chest pain (group 2 symptomatic ischemia), with 31

diabetic patients without ischemic ST depression or chest pain (group 3 no ischemia) and with 429 patients without diabetes who had silent ischemia during exercise testing. All patients had documented coronary artery disease (CAD) (70% diameter narrowing). The 6-year survival among patients with silent ischemia was worse in diabetic than non-diabetic patients.

A similar study of 58 asymptomatic male diabetics without prior evidence of CAD were evaluated with 24 hr. holter monitoring, exercise ECG, Thallium scintigraphy, autonomic tests and pain threshold measurement. They found that 36% had autonomic dysfunction and 17% had myocardial ischemia, which was more common in those with autonomic dvsfunction than those with normal autonomic function (38% vs 5%,). There was no difference in the somatic pain threshold.

In another instance 40 consecutive diabetics on exercise ECG, autonomic testing and coronary angiography were studied[24]. They found 37.5% to have silent ischemia with those with autonomic dysfunction having a greater prevalence of silent myocardial ischemia than those without (76.9% vs 25%).

One study[25] from India, evaluated 47 asymptomatic diabetics who underwent exercise ECG and autonomic function testing. 63.8% had >1 autonomic test abnormal and 46.8% had >2 autonomic tests abnormal.

38.3% had abnormal responses on TMT and those with autonomic dysfunction had a greater prevalence of silent ischemia than those without (59% vs 20%). Further, to validate the results coronary angiography was carried out in 9 patients who were TMT positive and 4 patients who were TMT negative. 8/9(88%) of the former and 1/4 (25%) of the later demonstrated significant coronary stenosis.

Another study[26] from India evaluated 20 male diabetic patients (age range, 40-60 years) with normal autonomic function were to determine the prevalence of silent myocardial ischemia on exercise as well as ambulatory electrocardiography. The presence and extent of silent myocardial ischemia was also correlated with the severity of atherosclerotic coronary artery disease as determined by coronary angiography. A cohort of 20 matched non-diabetic patients was also included in the study. Silent myocardial ischemia was detected in 50% of the diabetic patients on exercise electrocardiography and in 35% on ambulatory electrocardiography compared with 10% and 5% in non-diabetics by the two methods, respectively. On exercise testing in diabetic patients, silent myocardial ischemia was detected in 64% of the patients with three-vessel disease; 50% of the patients with two-vessel disease and 20% of the patients with one-vessel disease whereas in non-diabetic patients silent myocardial ischemia was detected in only 18% of the

patients with three-vessel disease and in none of the patients with two-or one-vessel disease. On ambulatory electrocardiography, only patients with three-vessel disease manifested silent myocardial ischemia. Thus, silent myocardial ischemia occurs in diabetic patients with coronary artery disease more frequently even in the absence of autonomic dysfunction and the prevalence of silent myocardial ischemia is higher in patients with severe degree of coronary artery disease.

One group[27] evaluated the prevalence of silent myocardial ischemia in 925 non insulin dependent diabetes mellitus patients, aged 40 to 65 years, asymptomatic, free from known coronary artery disease, advanced diabetic retinopathy and nephropathy with exercise electrocardiogram and thallium scintigraphy. The exercise tests were abnormal in 112 patients (12.1%), of whom 59 (6.4%) had perfusion defects at thallium scintigraphy. Multivariate analysis showed that the associated independent risk factors were age, total cholesterol, proteinuria and ST-T abnormalities on electrocardiogram.

Another group[28] from India studied 30 asymptomatic myocardial ischemia in unselected middle aged diabetics and controls by holter monitoring, tread mill test and coronary angiography. ST segment depression was seen in 14 (46.7%) out of 30 diabetics and in 3 (10%) out of 30 controls on both holter and tread mill test (p=0.002). Coronary

angiography done in patients with silent myocardial ischemia revealed higher prevalence of multi vessel involvement and diffuse disease in diabetics as compared to controls.

In one more study[29] from India, 120 asymptomatic stable type 2 diabetics were assessed for the presence of silent myocardial ischemia by using TMT. They found that 51(42.5%) had evidence of myocardial ischemia on TMT, of these 18 underwent coronary angiography and significant CAD was found in 15(83.7%).

In the Detection of Ischemia in Asymptomatic Diabetics (DIAD)[30] study,301123 patients with type 2 diabetes, aged 50-75 years, with no known or suspected CAD were randomly assigned to stress testing .The prevalence of ischemia in 522 patients randomized to stress testing were assessed myocardial perfusion imaging. A total of 113 / 522 patients (22%) had silent ischemia. The strongest predictors for abnormal tests were abnormal vasalva (odds ratio =5.6), male sex (2.5) and longer duration of diabetes (5.2).

In a study[31] including 500 patients with type 2 diabetes with no evidence of CAD on resting ECG found that 62(12.4%) patents exhibited abnormal changes on tread mill exercise test. CAD was diagnosed in 53 individuals by coronary angiography. The abnormalities of exercise test

were associated with the age of patients or the duration of diabetes ($p<0.05$).

ETIOPATHOGENESIS OF CAD IN DIABETES

The pathogenesis of CAD in diabetes is multifactorial; hyperglycemia, hyperinsulinemia, insulin resistance, dyslipidemia, hypercoagulability and inflammation contributes to the etiology of CAD in diabetes. The most important structure in a blood vessel which bears the brunt of various pathogenic processes is the endothelial cell. Endothelial dysfunction is an early event in atherogenesis and may be seen long before any morphological changes demonstrated in the arterial wall. Endothelial injury may be a common pathway for various risk factors such as smoking, dyslipidemia and hypertension which produce endothelial cell dysfunction and produce vascular disease. Endothelium provides a non- permeable barrier to smooth flow of blood and its cellular components which do not adhere to the intact healthy endothelium. Various immune inflammatory process leading to endothelial injury produce a cascade of events which are summarised below [32,33]

Cascade of events leading to endothelial injury:

1. Endothelial injury with resultant increased permeability.
2. Migration of various cells into the subendothelial tissue.
3. Adherence of platelets to the subendothelial collagen.

4. Migration of macrophages into subendothelium and formation of foam cells forming fatty streaks.
5. Smooth muscle cell proliferation and plaque formation.
6. Platelet aggregation leading to thrombogenesis.
7. Vascular occlusion.

SILENT MYOCARDIAL ISCHEMIA

Ischemic chest pain is blunted in DM. The myocardial ischemia or infarction may be associated with mild symptoms or may be totally silent. In the Framingham study group 25% of the myocardial infarctions were unrecognized. Silent infarctions are more common in diabetes (39%) when compared to non diabetics (22%). Healed scars on the myocardium in the absence of ante-mortem history of infarction are 3 times more common on autopsy studies in diabetics than in non-diabetics. Similarly during treadmill exercise test, angina is absent during ischemic episodes (painless ST depression) almost twice in diabetics than in non-diabetics 75% Vs 35%) and is due to severe autonomic neuropathy. Patients with diabetes who do experience angina became aware of their symptoms later in the course of ishcemia than do patients without diabetes. The delay in time from the onset of ST depression to angina may be twice as long to patients with diabetes than in patients without diabetes and correlates with the extent of autonomic nervous dysfunction. The incidence of

severe disease of the left main coronary artery is also significantly higher in diabetic than nondiabetic patients (13% Vs 6%).[38]

Mechanism of Anginal Pain

Anginal pain is frequently insufficiently sensitive. Pain stimuli arise with in the myocardium and most likely stimulate free nerve endings in the vicinity of small coronary vessels. Impulses travel in afferent unmyelinated (or) small myelinated cardiac sympathetic nerves though the upper 5 thoracic sympathetic ganglia to dorsal horn cells and through the spinothalamic tract to the thalamus and then to the cortex. At the cortical level, psychosocial and cultural factors may modulate the perception of pain.[40]

Diabetic patients have an increased incidence of painless Ml that is likely due, in part, to cardiac autonomic neuropathy. They have an increased prevalence, relative to non-diabetic patients of silent ischemia on exercise testing and ambulatory ECG monitoring.

Cardiovascular autonomic neuropathy

The development of symptomatic autonomic neuropathy in diabetics is an ominous sign with mortality over 50 per cent, three years after its onset. Generally parasympathetic fibers are affected first, leading to a relative increase in sympathetic tone that results in tachycardia and attenuation of the expected increase in heart rate and blood pressure with

exercise. An absence of parasympathetic tone may worsen ischemia. Sympathetic nervous system dysfunction is usually evident within five years of the diagnosis of parasympathetic dysfunction. Postural hypotension is the classical clinical manifestation of sympathetic dysfunction. [2,37,40,41,42,43]

Autonomic dysfunction in diabetes is multifactorial and may result from hyperglycemia-increased activity in the polyol pathway, altered myoinositol metabolism and non-enzymatic glycation. Other less understood mechanisms are alterations in nerve growth factor activity, blood viscosity, circulating platelets, transport of intraaxonal proteins and interaction between these pathways. The rationale for prevention of autonomic failure in DM is primarily to avoid sudden death in individuals with cardiovascular autonomic neuropathy during the metabolic demands imposed by anesthesia, surgery, physical, chemical or vascular stress, infection and exercise.

Cardiac autonomic neuropathy in DM manifests as postural hypotension, painless Ml or even sudden cardiac death and is associated with high mortality. Cardiac autonomic neuropathy may be associated with dysautonomic neuropathy, gastroparesis, diabetic enteropathy, prolonged ileus, neuropathic bladder, impotence and sweating disorder. Autonomic neuropathy may be responsible for sudden death in persons

with diabetes due to arrhythmia secondary to silent myocardial ischemia A relation exists between diabetic cardiac autonomic neuropathy and a prolonged QT interval on the ECG, which may predispose to life threatening ventricular arrhythmia.

Autonomic neuropathy may lead to ischaemia or infarction by several routes:

1. By increasing myocardial demand for oxygen by increasing resting heart rate.
2. By reducing myocardial blood flow by increasing coronary vascular tone at the site of the coronary stenosis.
3. By reducing coronary perfusion pressure during orthostatic hypotension.

CLINICAL TESTS OF AUTONOMIC FAILURE

Cardiovascular Reflexes

The tests described by Ewing are simple, not taking more than 20 minutes and do not require elaborate equipment. Tests employing heart rate responses are mainly parasympathetic and tests measuring B.P. responses are mostly sympathetic.

1. Heart rate responses (parasympathetic)

a. Heart rate response to valsalva maneuver.

b. Heart rate response during deep breath.

c. Heart rate response to standing.

2. Blood pressure test

a. Blood pressure response to standing.

b. Blood pressure response to sustained handgrip.

CAD in diabetes : Evaluation of myocardial ischemia[36]

CAD is a common cause of premature morbidity and mortality in diabetics. Evaluation of asymptomatic CAD in them is always a key issue. Early detection of CAD is therefore of paramount importance. Myocardial ischaemia may be asymptomatic or silent in a patient with known CAD, of the total ischaemic episodes only 20 to 30% are symptomatic and remaining 60 to 70% are silent, popularly known as silent myocardial ischemia (SMI). The occurrence of cardiac autonomic neuropathy dampens symptomatic episodes, making detection of SMI more crucial.

ADA Consensus Guidelines for Cardiac Stress Testing in Diabetic Patients[5]

Testing for CAD is warranted in patients with the following:

- Typical or atypical cardiac symptoms

- Resting electrocardiogram (ECG) suggestive of ischemia or infarction
- Peripheral or carotid occlusive arterial disease
- Sedentary lifestyle, age ≥35 years, and plans to begin vigorous exercise program

Asymptomatic individuals

Two or more of the risk factors listed below (a–e) in addition to diabetes:

a) Total cholestrol ≥240mg/dl, LDL ≥160mg/dl, or HDL ≤35mg/dl
b) Blood pressure >140/90mmHg
c) Smoking
d) Family history of premature CAD
e) Positive micro/macroalbuminura

Evaluation of coronary artery disease

1. Resting ECG
2. Ambulatory ECG monitoring
3. Stress test:
   - Stress electrocardiography
   - Stress Echocardiography
   - Pharmacological stress echocardiography
   - Stress Thallium

4. Coronary angiography

5. Intracoronary vascular ultrasound

The evaluation also includes other tests to evaluate associated risk factors like dyslipidemia, hypertension, glycosylation, coagulable state and platelet function.

Resting ECG

In diabetics, the resting ECG is normal in approximately one half of patients with chronic stable angina. In diabetics most common ECG abnormalities are non specific ST-T change with or without evidence of prior MI.

There are numerous pitfalls in using resting ECG in diagnosis of myocardial ischemia in patients with diabetes. ST-T wave abnormalities are seen in common general population with an overall prevalence of 8.5 percent for men and 7.7 %for women in the Framingham heart study. The prevalence increases with increasing age in the subjects with hypertension (HTN) and diabetes, in cigarette smokers and also in women. As the sensitivity and specificity of the resting ECG changes in patients with angina in diabetes is low, it cannot be relied to evaluate diabetes and angina with or without symptoms. A normal resting ECG does not exclude the presence of CAD. Severe triple vessel disease may exist with a normal resting ECG. A variety of conduction disturbances

like left anterior fascicular block or LBBB may be seen in asymptomatic diabetics. These are often associated with poor ventricular function in diabetic heart disease with or without clinical myocardiàl ischemia. LVH on ECG may suggest associated hypertension in diabetes.

Ambulatory 24 hrs electrocardiography

It is used to detect Silent Myocardial Ischaemia (SMI) or ventricular arrhythmias in diabetic patients with suspected or established CAD and myocardial ischemia..

Ambulatory (Holter) electrocardiography technology

The clinical utility of the ambulatory EGG recording lies in its ability to continuously examine a patient over an extended period of time, permitting patient ambulatory activity and facilitating the diurnal electrocardiographic examination of a patient in a changing environmental milieu (both physical and psychological).

STRESS TESTING METHODS AND PROTOCOLS

Numerous devices have been used to provide the dynamic exercise for exercise testing, including steps, escalators and ladder mills. Today, however, the bicycle ergometer and treadmill are the most commonly used dynamic exercise devices.

MASTER'S TWO STEP TEST

This test of Master was originally constructed as an exercise tolerance test rather than a screening test for coronary disease. The patient is made to walk to the top of the standardized two step staircase (each 9 inches) and down the other side (18 inches). Then he turns round and climbs back the 18 inches step and gets down the two step staircase. This constitute one cycle. The patient now traverses the stairs proper number of times for his or her age and sex in 3 minute. A 12 lead ECG is taken before the test and lead V5 (or V4) should be sampled for 5-10 seconds every minute during exercise. The test is terminated when the patient completes the prescribed work load, or at the first appearance of chest pain, pallor or dyspnoea. The ECG is repeated. Master recommended that 0.5 mm of ST depression be accepted as abnormal. The most important limitation of Master's test is obviously that the amount of exercise given is usually insufficient and H.R. and BP are not measured during the test, thus no measurement is available to evaluate the percentage of maximum work.

HARVARD STEP TEST

This was developed in Harvard University Fatigue laboratory around 1940. It is basically an exercise tolerance test somewhat similar to the original master's test before the ECG was applied. The patient is

asked to step up and down on a 20 inch platform 20 times a minute for 5 minutes. Pulse is counted during the recovery period and by calculation Harvard score is obtained. The limitations are same as in the Master's test.

BICYCLE ERGOMETER

Bicycle ergometry has been widely used in Europe and South America. Dynamic exercise on a bike depends on the force applied as resistance to the pedals and the pedal rate. The bicycle may mechanically or electrically braked to increase the resistance. The advantages of the bicycle are that it is usually cheaper, takes up less space, and since upper body motion is reduced, it is easier to obtain BP measurements and obtain EGG. The patients body weight does not influence exercise capacity. In the opinion of Ellestad and many people in United States, treadmill applies a more physiologic workload and V02 max. values achieved were greater during treadmill exercise.

TREADMILL

The motor driven treadmill was introduced for clinical use in the 1950's. It is the most commonly used dynamic testing modality in the United States and India since most patients are more familiar with walking, than they are with bicycling. The use of treadmill presents a number of advantages because it is possible to adjust the speed and grade

of walking to the agility of the subject. The workload can be increased by increasing the speed and / or grade. The starting speed of 1.7 mph at a 10 percent grade recommended by Bruce and associates, resulting in an oxygen consumption of about 4 METs, has been very satisfactory. There are, however, reports of success with higher or lower speeds and inclines. The work load is better administered than with a bicycle ergometer since if the patient slows down he goes off the back of the treadmill. Despite these advantages, the treadmill presents several disadvantages. It is more expensive, occupies a considerably larger space, and is noisy, which makes it difficult to record BP and ECG at high speeds.

ARM EXERCISE TESTING

In subjects who are unable to exercise with their legs, because of orthopaedic problems or vascular insufficiency, arm ergometry provides an excellent substitute.

ATRIAL PACING

This test requires that a pacing catheter be placed in the right atrium. The correlation of heart rate and increased myocardial oxygen consumption indicates that at some heart rate, most patients with ischemic heart disease will have either chest pain or ischemic ST-segments.

DIPYRIDAMOLE TEST

In patients who cannot walk on treadmill because of osteoarthritis, neurological deficits, etc, stress can be induced by Dipyridamole infusion at rate of 0.75 mg/kg/mm, over 4 min. ECG is to be recorded during post infusion period for about 6-10 minutes and to be compared with pre-infusion ECG.

TREADMILL PROTOCOLS

The various protocols available for clinical use include an initial low load (warm up), and progressive increase in workload in stages. Though there are many protocols available for clinical use name will be ideal for every clinical situation. The suitability varies according to the objectives of the exercise test. For example, a vigorous exercise protocol may be suitable for screening a relatively healthy individual. On the other hand, a milder exercise protocol may be adequate for functional evaluation of a known cardiac patient and lighter workloads are needed for pre-discharge post infarction evaluation. Thus an ideal exercise protocol should have an initial workload well within a given individuals anticipated physical working capacity and the workloads, should be increased gradually and maintained for a sufficient length of time to achieve a near physiologic steady state.

BRUCE PROTOCOL

This is the most widely used protocol. It consists of 7 stages in which speed and grade are increased every 3 minutes. Bruce protocol has the advantage of being relatively short in duration. It also has many disadvantages. It's high work loads may not be suitable for most cardiac patients or elderly sedentary individuals. The large increments in work make the estimation of maximal oxygen consumption less accurate. The fourth stage can either be run or worked, which results in differing oxygen costs.

Stage	Speed (Km/Hr)	Grade (%)	Duration (Min)	METS
1	2.7	10	3	4-5
2	4.0	12	3	6-7
3	5.4	14	3	8-10
4	6.7	16	3	13-16
5	8.0	18	3	21
6	8.8	20	3	-
7	9.6	22	3	-

MODIFIED BRUCE PROTOCOL

This protocol to an extent overcomes the disadvantages of the Bruce protocol. Here the first two stages are run at 1.7 mph at 0% and 5% grades. The third stage of modified Bruce corresponds to 1st stage of Bruce. The remaining stages corresponds to that of Bruce protocol.

NAUGHTON'S PROTOCOL

In this protocol the workloads are increased every two minutes. The increments being small and gradual, this protocol is quite useful in post myocardial infarction stress evaluation.

Mc HENRY'S PROTOCOL

It also provides a small initial workload and gradual increase every 3 minutes.

MODIFIED BALKE-WARE PROTOCOL

This uses a constant brisk walking speed (3.4 mph) with 1% increase in grade every minute.

ELLESTAD PROTOCOL

In the Ellestad protocol, the speed is increased progressively every 2 or 3 minutes during 7 stages with constant grade of 10% for the first 4 stages and 15% for the last three stages.

In summary, it is important to individualize the protocol election for the patient being tested. The optimal protocol is 6 to 10 minutes in length, endurance is tested rather than aerobic capacity. Exercise capacity should be reported in METS, not minutes.

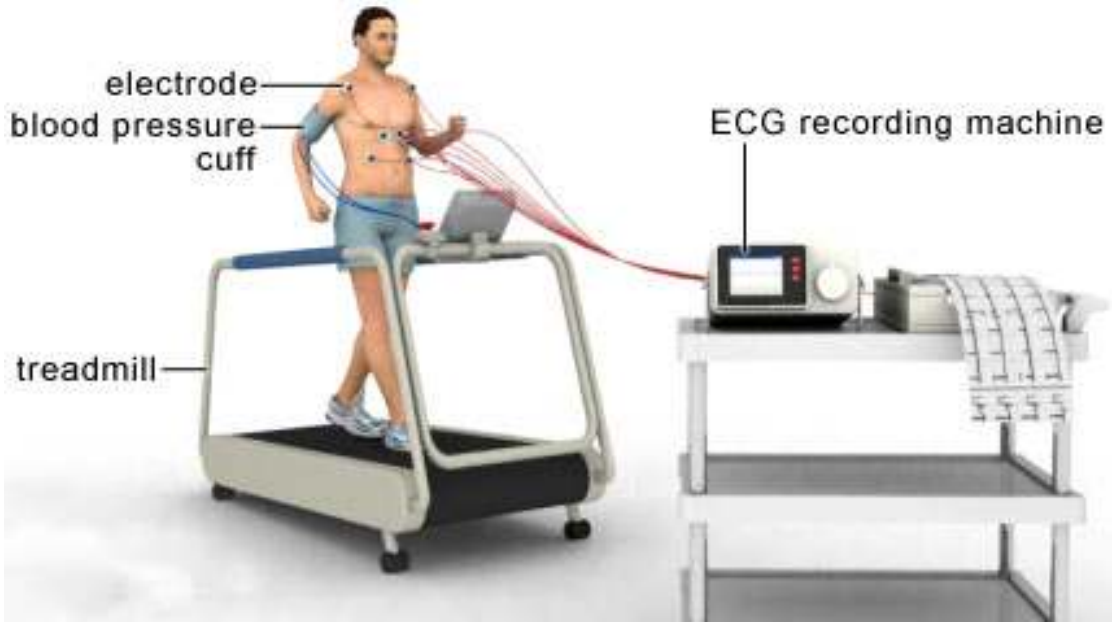


Fig 1 : Procedure of Treadmill

Fig 2 : Treadmill

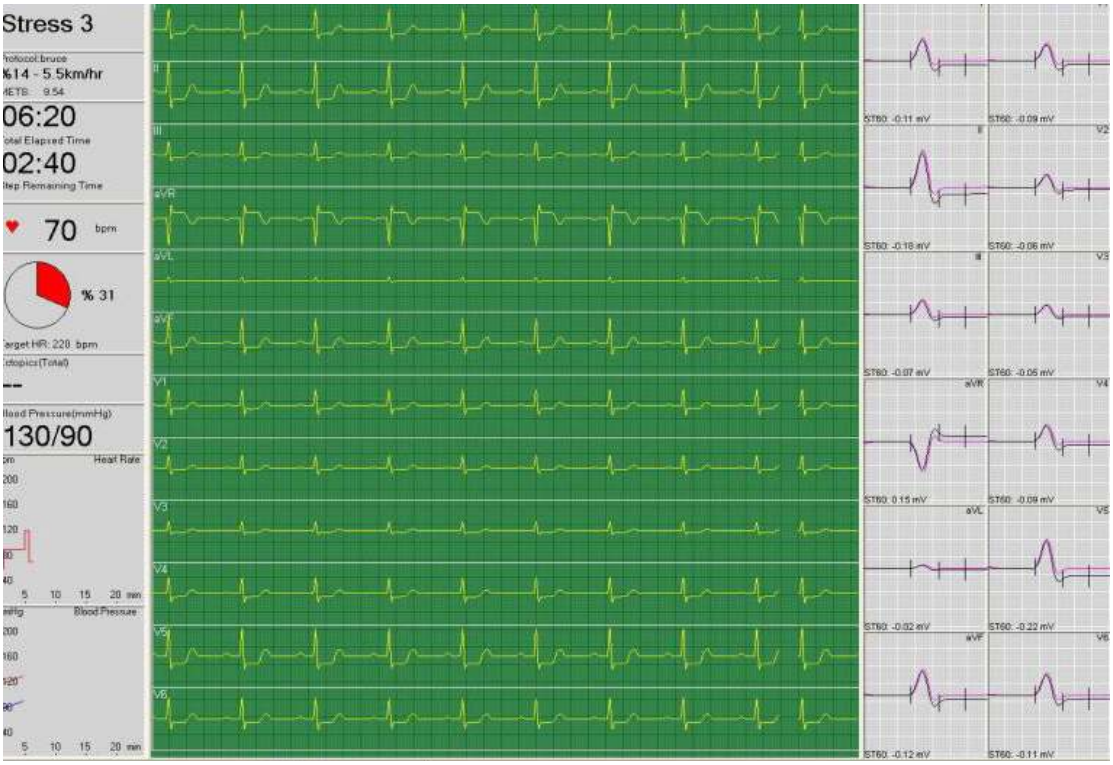


Fig 3 : Recordings of Stress ECG

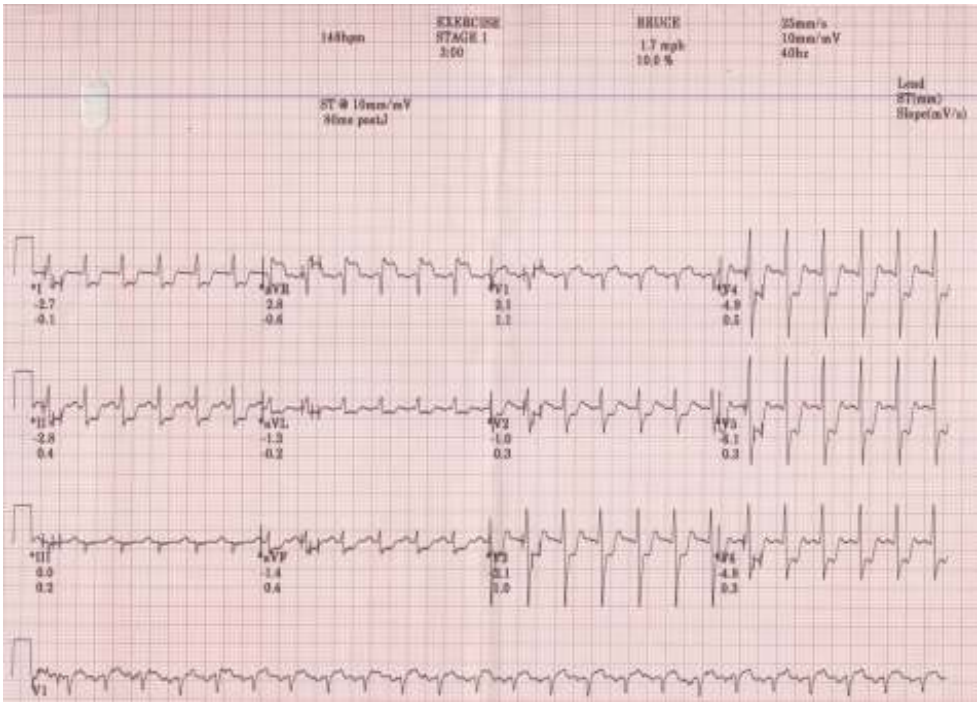


Fig 4 : Positive TMT Graph

GENERAL INDICATIONS FOR EXERCISE TESTING[3,37]

CLASS-I

1. Diagnosis of CAD in patients with symptoms or other findings that are suggestive, but not diagnostic of coronary disease.
2. To assess functional capacity and to aid in assessing the prognosis of patients with known CAD.
3. To evaluate the prognosis and functional capacity of the patients with CAD after an uncomplicated myocardial infarction (before discharge or early after discharge).
4. To evaluate after coronary artery revascularization by CABG or coronary angioplasty.
5. Evaluation of arrhythmias.
6. To evaluate functional capacity of selected patients with congenital heart disease.
7. To evaluate patients with rate-responsive pace makers.

CLASS-II

1. Screening for latent CAD in asymptomatic patients over the age of 40 with two or more risk factors for CAD.
2. Screening asympomatic patients over the age of 40 with special occupations (pilots, bus or truck drivers, rail road engineers etc).

3. To evaluate sedentary patients over the age of 40 who plan to enter a vigorous exercise program.
4. To evaluate patients with variant angina.
5. To evaluate functional capacity and response to drug therapy in patients with CAD or heart failure.
6. To evaluate patients who have sustained a complicated myocardial infarction but who have subsequently established (before or early after discharge).
7. Functional capacity of patients with valvular heart disease.
8. To follow up serially (at 1 year intervals or longer) patients with known CAD.
9. To evaluate on a routine, yearly basis patients who remain asymptomatic after a revascularization procedure.
10. To evaluate patients with resting ECG changes.

CONTRAINDICATIONS[3,32,37]

The exercise ECG test is associated with a very low morbidity or mortality rate when the test is directly supervised by an experienced physician. A reasonable knowledge of the patient's past medical history and present problems is essential. A fairly good idea of patient's capacity to exercise can be obtained when this information is combined with auscultation of the heart and inspection of the resting ECG. Then, by

carefully observing the patients response to early stages of the exercise protocol, the physician can be alerted to potential dangers and take steps to make certain that no harm is done.

GENERAL CONTRAINDICATIONS TO EXERCISE TESTING

Absolute contraindications

1. Recent acute myocardial infarction (generally < 6 days).
2. Unstable progressive angina (including angina at rest).
3. Severe symptomatic left ventricular dysfunction.
4. Potentially life threatening cardiac dysarrhythmias like ventricular and atrial tachyarrhythmias and advanced second or third degree AV block.
5. Acute pericarditis, myocarditis and endocarditis.
6. Severe aortic stenosis.
7. Acute pulmonary embolus or infarction.
8. Acute or serious general illness like acute infections, hyperthyroidism or severe anemia.
9. Patients with locomotive problems (amputation severe arthritis or deformity)
10. Acute thrombophlebitis or deep vein thrombosis.
11. Known severe left main disease (> 70%).
12. Severe resting hypertension (> 240/130).

RELATIVE CONTRAINDICATIONS

1. Any less serious non cardiac disorder (uncontrolled metabolic disease such as diabetes, myxoedema or thyrotoxicosis, asthma, hepatitis, pneumonic etc.)
2. Arterial hypertension (generally greater than 200 mmHg of systolic or 120 mmHg diastolic).
3. Moderate valvular or myocardial heart disease.
4. Known or suspected left main obstruction.
5. Hypertrophic cardiomyopathy with significant outflow obstruction.
6. Drug effect or electrolyte abnormalities (Digitalis intoxication, hypokalemia, tranquilisers, alcohol, disopyramide, quinidine, etc.)
7. Psychiatric disease.
8. Inability or lack of desire or motivation to perform the test.

SAFETY PRECAUTIONS AND COMPLICATIONS

SAFETY PRECAUTIONS

As mentioned earlier, exercise testing should be performed only by well trained person with a basic working knowledge of exercise physiology. Although exercise testing is considered a safe procedure, there are reports of acute infarctions and deaths occurring secondary to this procedure. Keeping these things in mind certain safety precautions have to be taken. They may be summarized as follows:

1. Complete history and physical examination.
2. Indications and contraindications should be carefully considered.
3. Informed consent obtained before the exercise test for medicolegal purposes.
4. It is essential to take 2 sets of complete 12-lead electrocardiograms. Pre exercise ECG and post exercise ECG.
5. ECG (preferably 12 lead ECG) monitoring continuously during and after exercise until completion of the test (usually 8-10 minutes during recovery period).
6. Proper skin preparations and good quality electrodes are important to avoid artifacts and problems of interpretations.
7. BP should be recorded before, during and after test (ideally every minute).
8. The indications for termination of the test should be known thoroughly.
9. It is essential to have all necessary cardiopulmonary resuscitative facilities in the exercise laboratory, including a defibrillator and commonly used cardiac drugs.

COMPLICATIONS

Although exercise testing is considered a safe procedure in experienced hands, it is not without inherent risks, and the complications can and do occur.

CARDIAC COMPLICATIONS

1. Hypotension and shock
2. Congestive heart failure
3. Severe cardiac dysarrhythmias
4. Myocardial infarction
5. Sudden death
6. Hypertension

NON CARDIAC COMPLICATIONS

1. Musculo skeletal pain
2. Cerebrovascular accidents
3. Phlebitis

CONDUCT OF EXERCISE TEST

PATIENT PREPARATION

Preparations for exercise testing include the following:

1. The patient should be instructed not to eat or smoke for 2 to 3 hours prior to the test and to come lightly dressed for exercise.

2. A complete history and physical examination should be accomplished to rule out any contraindications for exercise testing. [3]The use of certain medications like digitalis, beta blockers, calcium channel blockers, nitrates, which interface with the result of the exercise test should be curtailed wherever possible. In most of the exercise laboratories, drug therapy is withdrawn 24 to 48 hours before performing the test.

4. A resting 12 lead ECG should be obtained. This is important because detection of changes of acute MI may prohibit testing and detection of LBBB, LVH and WPW syndrome etc may make the interpretation more difficult. Another ECG should be recorded during 20-30 seconds of hyperventilation as this procedure can produce ECG changes similar to ischemic patients. Appearance of such changes suggest the increased possibility of false positive test results.

5. Informed consent should be obtained after explaining the possible risks involved in exercise testing.

6. The testing procedure should be carefully explained to the patient and treadmill walking should be demonstrated.

7. Skin preparation and electrodes placement: The proper skin preparation is essential for obtaining high quality ECG recordings.

The removal of superficial keratinised layer is the most important factor. The areas for electrode applications are first rubbed with an alcohol or acetone saturated guaze (after shaving hairy chest) to remove the superficial only layer. Then these area re rubbed with fine sand paper or rough material to obtain good electrode contact. This reduces the contact impedance from 10-50 k. ohms to 1-5 k ohms. The most reliable electrodes are light weight liquid contact silver chloride electrodes. Since a standard 12 leads ECG with electrodes placed on the limbs could not be obtained during exercise, other electrode placements have been used. The arm electrodes and lower limb electrodes are brought on to the trunk and placed at sites nearest to the respective limbs. This modified placement (Mason-Likar modification) lessening the motion artifact without producing much difference from the standard 12 lead ECG.

END POINTS

TARGET HEART RATE APPROACH

Many exercise laboratories employ submaximal tests, in which target heart rate and points correspond to 85 to 90% of the predicted maximal heart rate observed in normal subjects (220 - age in years). The test is terminated prematurely if there are an other indications for stopping the test. The submaximal testing is often predicted on the

mistaken assumption that such a testing is safer than symptom limited testing. However, the poor relationship between maximal heart rate and age must be understood. The THR approach has major limitations in patients receiving beta adrenergic blocking agents and in those with heart rate impairment on exercise heart rate response.

SYMPTOM LIMITED TESTING

This is performed in almost all circumstances except very soon (i.e., 10-14 days) after acute cardiac events such as myocardial infarction and CABG surgery symptom limited testing has been safely performed as soon as 72 hours after the last episode of chest pain in patient's admitted to hospital for unstable angina (MI ruled out).

INDICATIONS FOR TERMINATION OF EXERCISE TEST[37]

In a patient with known or suspected heart disease, the physician administering the test must continuously observe the patient and the monitor. The electrocardiographic printout is often more informative than the image on the oscilloscope and must be available for immediate infarction whenever needed.

The indications for termination of an exercise tests have been summarized below:

1. Anginal pain is progressive.

2. Drop in systemic blood pressure below the resting value or non raising SBP with continued exercise. A fall of more than 20 mmHg in systolic pressure occurring after the normal initial rise.

3. Frequent premature ventricular contractions developing in pairs or with increasing frequency as exercise increases or ventricular tachycardia and ventricular fibrillation development.

4. Atrial tachycardia, atrial fibrillation or atrial flutter supervenes.

5. Hypertensive response of SBP>280 mmHg and diastolic BP > 140 mmHg.

6. Onset of second or third degree heart block.

7. ST segment depression has become marked. Most would terminate the exercise at 3mm or more ST depression.

8. ST segment elevation of 2 mm or more.

9. Patient is unable to continue because of dyspnoea fatigue or feeling of faintness or dizziness.

10. Signs of poor perfusion like pallor, cyanosis and cold extremities and sweating.

11. Marked apprehension, mental confusion or lack of coordination.

12. Technical problems with monitoring the ECG or systolic blood pressure.

13. Patient's request.

14. Development of bundle branch block that cannot be distinguished from ventricular tachycardia.

15. When the patient has reached or exceeded the predicted maximal heart rate, one can be satisfied that the patient has performed satisfactorily. However, if the subject is able and willing to continue, one can safely proceed if there are no other indications for termination. Patients should understand that they can stop voluntarily, but are encouraged to try to reach or exceed maximum predicted heart rate. When performed in patients with a high likelihood of coronary artery disease, the positive and negative predictive values of exercise testing are high, with a sensitivity and a specificity ranging from 60% to 90%.[37]

Materials & Methods

MATERIALS AND METHODS

The present study was conducted in the CMC Hospital, Coimbatore during the period of September 2009 to september 2010.

Study Design

One year cross sectional study on the patients of type 2 diabetes mellitus without any clinical and electrocardiographic evidence of coronary artery disease.

Source of data

The patients of type 2 diabetes mellitus without clinical evidence of coronary artery disease attending diabetic clinic and medicine OPD, CMC Hospital, Coimbatore were enrolled in the study.

Sample Size

Total of 50 patients included in the study.

Inclusion Criteria

1. Patients of type 2 diabetes mellitus without clinical evidence of CAD
2. Normal resting 12 lead ECG
3. No past history of ischaemic heart disease, CVA and hypertension.

Exclusion Criteria

1. Patients having symptoms and signs suggestive of ischaemic heart disease.
2. Abnormal resting 12 lead ECG
3. Presence of risk factors known to predispose to ischaemic heart disease.
    a. Hypertension.
    b. Evidence of CAD
    c. Vascular disease (Cerebrovascular accident, peripheral vascular disease).
    d. Cigarette smoking.
    e. Patients on oral contraceptive pills.

Methods and collection of Data

All the patients attending to diabetic clinic and medicine OPD, CMC Hospital, Coimbatore were screened for eligibility. The eligible patients were given an informed consent. The consented participants were enrolled in the study. Descriptive data of the participants like name, age, sex, personal history, occupational, were obtained by interviewing the patients. Each of the patient's proper history were recorded on predesigned and pretested proforma. They underwent a thorough physical examination.

HISTORY AND EXAMINATION

A detailed history was elicited from all patients with emphasis on duration of diabetes mellitus, symptomatology of diabetes mellitus and its various microangiopathic complications.

Body mass index (BMI) was calculated according to Quetelet's formula and subjects accordingly categorized.

Type	BMI Kg/m^2
Normal	18.5 – 24.9
Overweight	25 – 29.9
Obesity	30 – 39.9
Morbid obesity	>40

A meticulous systemic examination was conducted in all patients including fundus examination to find diabetic retinopathy and special emphasis was laid on autonomic neuropathy.

Tests for autonomic neuropathy

1) Resting heart rate > 100 beats/min is abnormal

2) Beat-to-beat heart rate variation

With the patient at rest and supine (no overnight coffee or hypoglycemic episodes), breathing 6 breaths/min, heart rate monitored, a difference in heart rate of > 15 beats/min is normal and < 10 beats/min is abnormal.

3) Systolic blood pressure response to standing

Systolic blood pressure is measured in the supine subject. The patient stands and the systolic blood pressure is measured after 2 min. Normal response is a fall of < 10 mmHg, borderline is a fall of 10-29 mmHg, and abnormal is a fall of > 30 mmHg with symptoms.

Autonomic dysfunction defined as 2 or more abnormal responses.

INVESTIGATIONS

All patients were subjected to the following investigation at the time of inclusion into the study.

- Routine hemogram
- Fasting and post prandial blood sugar
- Glycosylated hemoglobin
- Lipid profile(total cholesterol, triglycerides, LDL, HDL)
- Blood urea and serum creatinine
- Urine routine and microscopic examination
- X-ray chest (PA view)
- Resting Electrocardiogram
- Tread mill testing

Technique of treadmill test

The patient is instructed not to eat or drink caffeinated beverages three hours prior to testing and to wear comfortable shoes and loose

fitting clothes. A brief physical examination performed prior to the test and a written informed consent taken. A standard 12 lead ECG taken following which a torso ECG obtained in the supine position and in the sitting or standing position. Blood pressure recorded in both positions and the patient instructed on how to perform the test. Standard multistage maximal exercise test done on a motorised treadmill according to Bruce protocol. The heart rate, blood pressure and electrocardiograms recorded at the end of each stage of exercise, immediately before and after stopping the exercise and for each minute for at least 5 to 10 minutes in the recovery phase. Exercise test terminated in all patients following the achievement of target heart rate or an abnormal ischemic response. This is defined as development of 0. 10 mV (1mm) of J point depression measured from the PQ junction, with a relatively flat ST segment slope (<lmV/sec), depressed ≥ 0.10 mV 60 to 80 msec after the J point in three consecutive beats with a stable baseline. Exercise test also terminated if patient develops dysponea, fatigue or chest pain

Results and Analysis

RESULTS & ANALYSIS

DATA ANALYSIS

A total number of 50 cases of type 2 diabetes mellitus without clinical and ECG evidence of CAD were studied and the following observations were noted.

Age

The mean age of the study subjects was 50.56 years; standard deviation (SD) of 7.59 years. Most of the patients belonged to the age group 40 – 60 years.

Sex

Out of 50 cases, 40 were males and 10 were females. The ratio of males to females was 4:1.

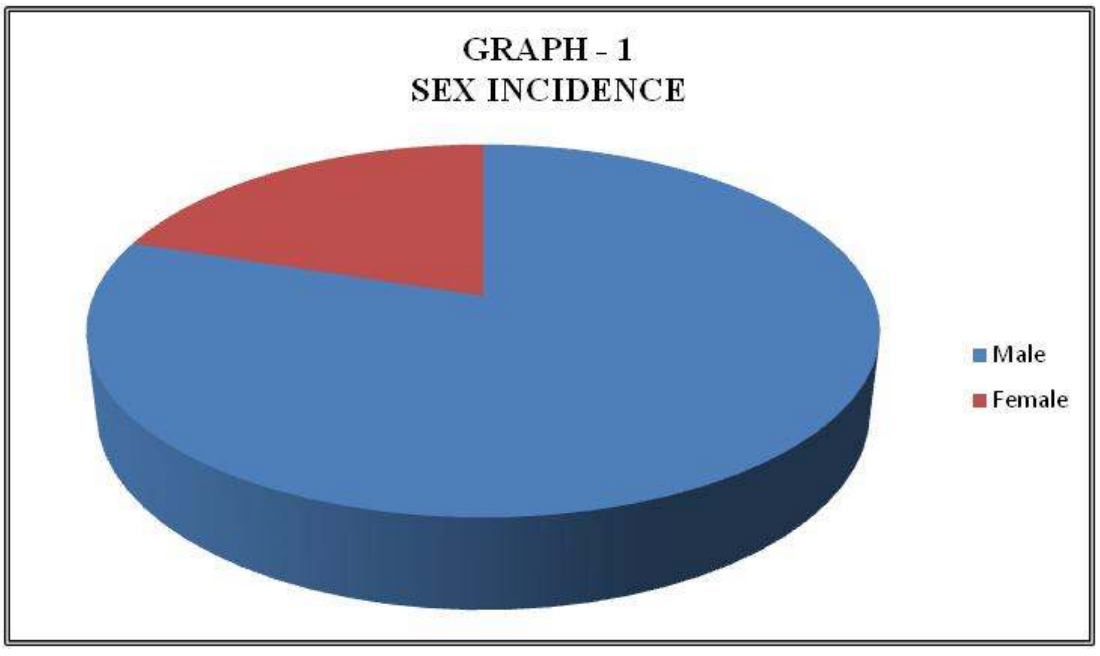
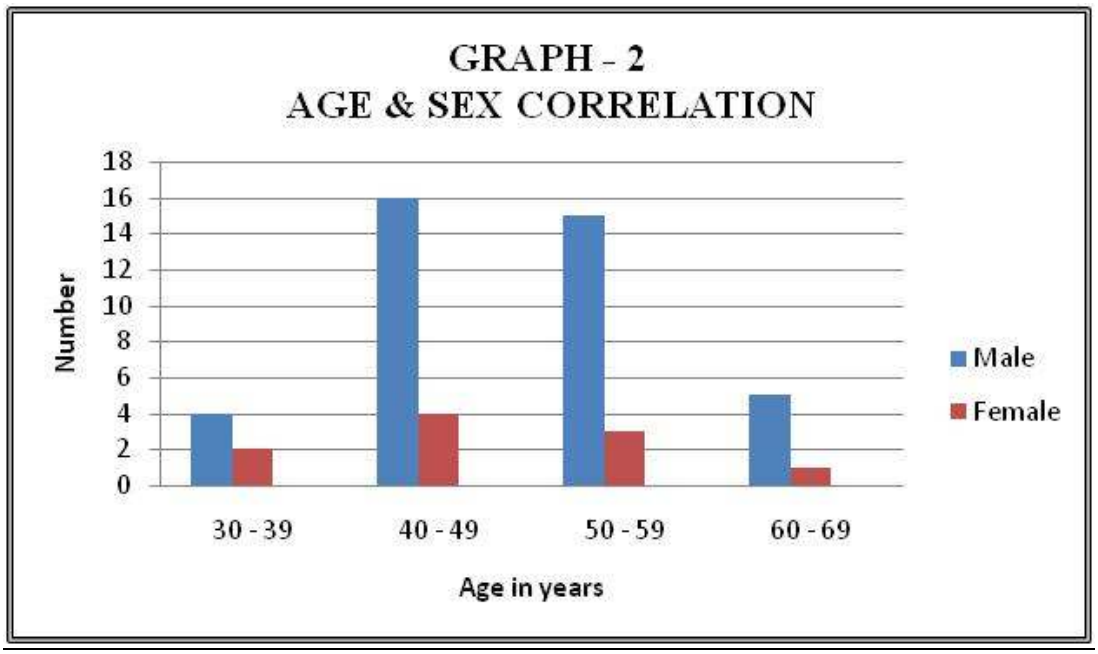


TABLE - 1

AGE AND SEX CORRELATION

Age in years	Male	Female	Total
30-39	04	02	06(12%)
40-49	16	04	20(40%)
50-59	15	03	18(36%)
60-69	05	01	06(12%)
Total	40	10	50 (100%)



6 patients (12%) in the study were in the age group of 30 – 39 years. Of these 4 were males and 2 were females . 20 patients (40%) were in the age group of 40 – 49 years. Of these 16 were males and 4 were females. 18 patients (36%) in the study were in the 30 – 59 age group, of

these 15 were males and 3 were females. 6 patients (12%) were in the age group of 60 –69 years, of these 5 were males and 1 was female. Most patients were between the age group of 40-60 years.

TABLE - 2

PARAMETERS

S No.	Parameter	Males n=40		Females n=10		P value	Inference
		Mean	SD	Mean	SD		
1	Age in yrs	50.78	7.45	49.70	8.47	0.69	NS
2	BMI(kg/m^2)	25.30	4.08	23.4	5.50	0.24	NS
3	Pulse per mt	79.05	7.81	77.5	5.19	0.55	NS
4	SBP mm Hg	132.40	7.00	130	7.24	0.35	NS
5	DBP mm Hg	83.35	6.46	84	6.99	0.78	NS
6	HBA1C %	8.61	1.11	8.86	2.02	0.60	NS
7	TCholesterol	191.05	34.23	187.3	32.21	0.7554	NS
8	TGL	135.83	36.84	130.7	51.35	0.7184	NS
9	LDL	127.88	29.22	126.00	23.75	0.8520	NS
10	HDL	36.03	3.53	35.10	3.60	0.4636	NS
11	FBS	162.87	45.67	163.90	25.53	0.94	NS
12	PPBS	216.97	66.03	229.40	53.43	0.58	NS

Statistically, no significant difference was seen between the sexes as far as their mean age, BMI, Pulse, Systolic blood pressure, Diasolic blood pressure, HbA1C, Total cholesterol, Triglycerides, LDL, HDL, FBS and PPBS was concerned

TABLE - 3

BODY MASS INDEX

BMI	No: of patients	Percentage
Normal(18.5 – 24.9)	29	58%
Overweight (25 – 29.9)	16	32%
Obese (30 – 39.9)	5	10%
Total	50	100%

29 (58%) patients were with normal body mass index, 16 patients (32%) were overweight while only 5 (10%) patients were obese.

TABLE - 4

DURATION OF DIABETES MELLITUS

Duration of DM	Male	Female	Total
≤5	25 (62.5%)	05 (50%)	30 (60%)
6-10	08 (20%)	02 (20%)	10 (20%)
11-15	06 (15%)	01 (10%)	07 (14%)
16-20	01 (2.5%)	02 (20%)	03 (06%)
Total	40 (100%)	10 (100%)	50 (100%)

In the study population, more number of patients (30 i.e. 60%) were having diabetes equal to or less than 5 years, followed by 10 patients (20%) with the duration of 6 to 10 years, next 7 patients (14%) between 11 to 15 years and only 3 patients(6%) between 16 to 20 years.

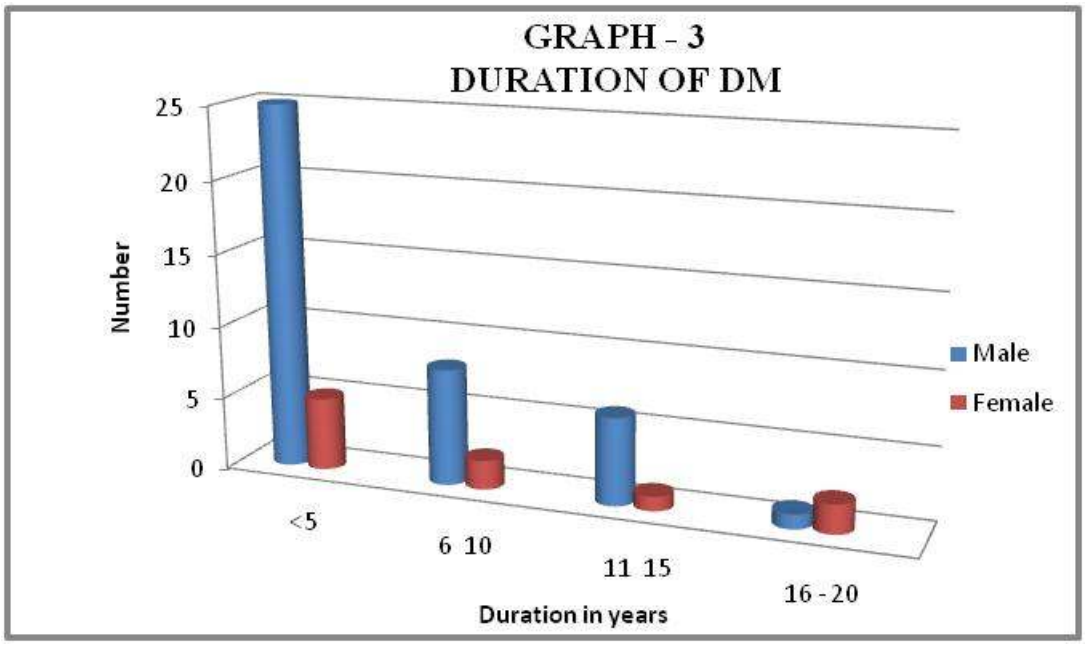
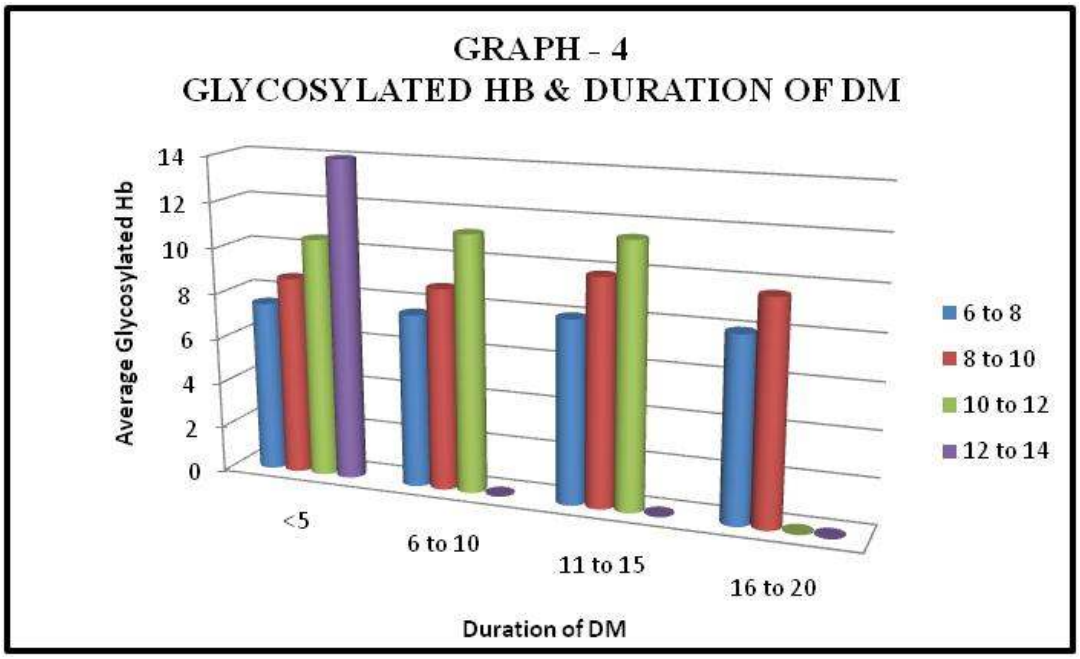


TABLE - 5

GLYCOSYLATED HEMOGLOBIN AND DURATION OF DIABETES MELLITUS

Duration of DM	Average Glycosylated Hemoglobin				
	6-8	8-10	10-12	12-14	Average
<5	7.50	8.70	10.5	14	8.50
6-10	7.58	8.80	11.2	-	8.55
11-15	8.0	9.85	11.45	-	9.36
16-20	8.0	9.60	-	-	9.07

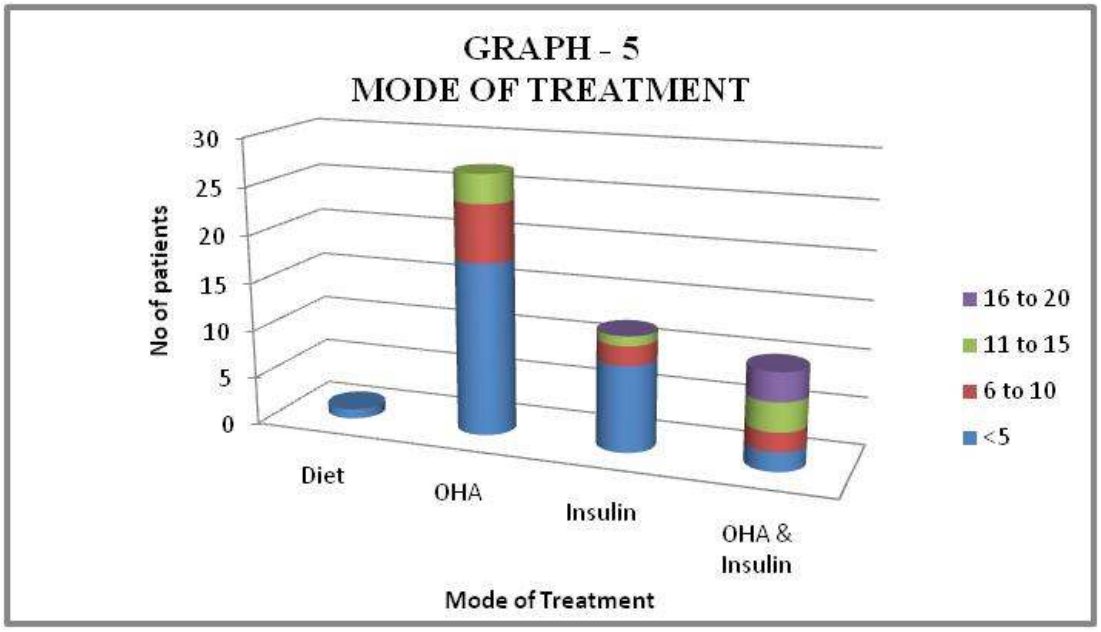


The average glycosylated hemoglobin (HbA1C) was 8.50, 8.55, 9.36 and 9.07 for the duration of diabetes equal to or less than 5 yrs ,6 to 10 yrs, 11 to 15 yrs and 16 to 20 yrs respectively. This shows that all patients had poor glycaemic control.

TABLE - 6

MODE OF TREATMENT

Duration of DM	Diet	OHA	Insulin	OHA & Insulin	Total
<5	01	18	09	02	30
6-10	-	06	02	02	10
11-15	-	03	01	03	07
16-20	-	-	-	03	03
Total	01 (02%)	27 (54%)	12 (24%)	10 (20%)	50 (100%)

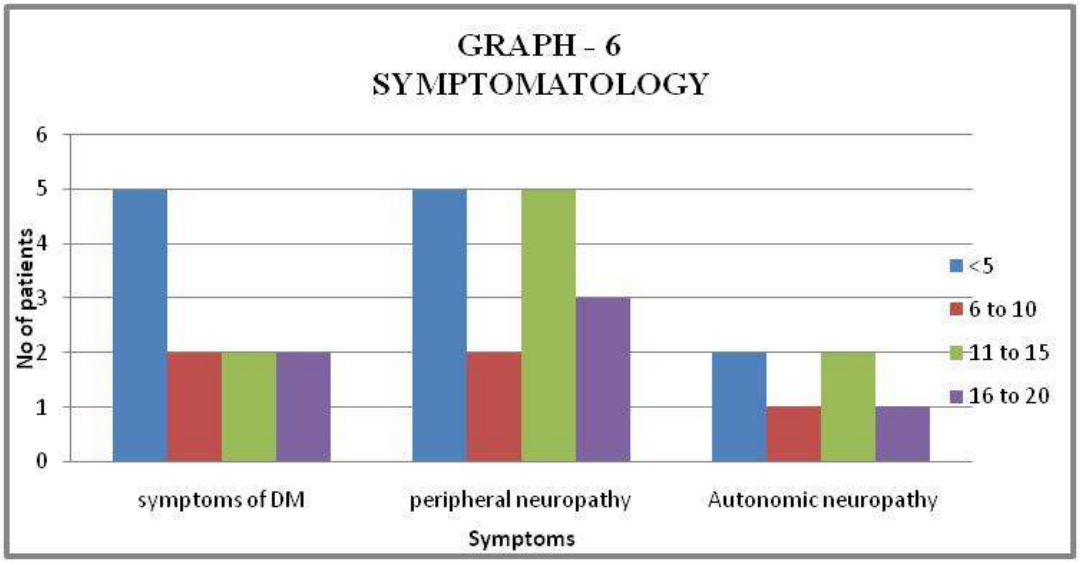


In 50 patients, 1(2%) was on diet control alone, 27 (54%) were on one or the other OHA's, 12 (24%) were on one or the other form of insulin while 10 (20%) were receiving both oral hypoglycaemic agents and insulin.

TABLE - 7

SYMPTOMATOLOGY

Duration of DM	Symptoms of DM	Symptoms of Peripheral Neuropathy	Symptoms of Autonomic Neuropathy
≤5	05	05	02
6-10	02	02	01
11-15	02	05	02
16-20	02	03	01
Total	11	15	06



This table depicts the symptoms of diabetes and microangiopathic complications of the study population at the time of inclusion into the study. Of the 50 patients only 11 (22%) had symptoms of diabetes, 15 (30%) had symptoms of peripheral neuropathy while only 6 (12%) had symptoms of autonomic neuropathy. None of the patients had symptoms of nephropathy and retinopathy.

TABLE - 8

BLOOD LIPID PROFILE

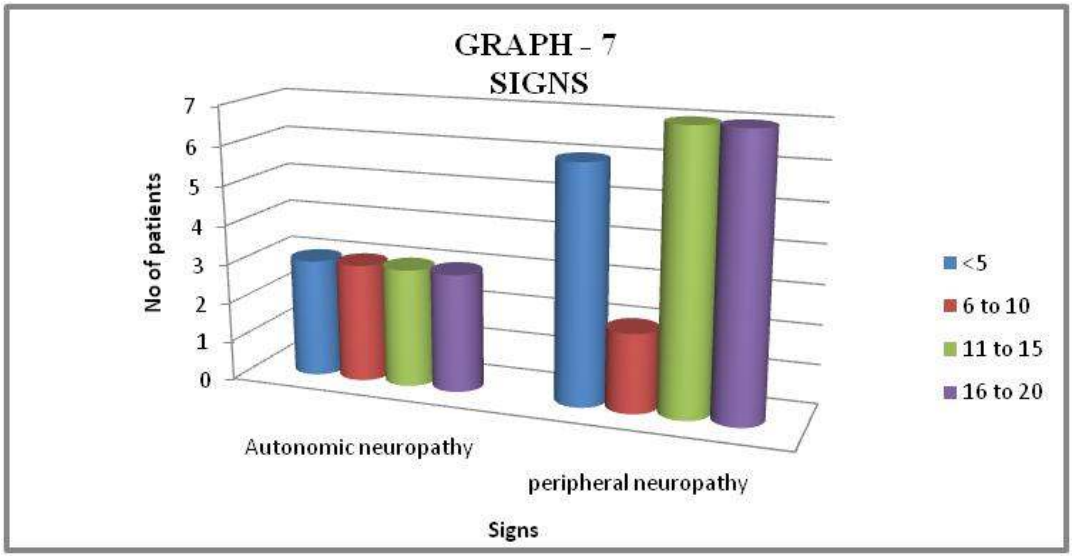
Duration of DM	Av.Cholesterol		Av. TGL		Av. HDL		Av. LDL	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<5	183.50	29.75	131.6	32.94	121.30	25.78	35.87	3.23
6-10	190.80	28.64	123.3	32.03	130.40	23.78	35.8	3.49
11-15	197.14	45.20	142.86	57.94	132.29	33.76	36.29	4.96
16-20	240.67	16.01	186.33	54.59	168.67	18.93	34.67	4.62

This table shows the blood lipid profile of the study subjects. Statistically there was no significant difference in average cholesterol, tryglicerides, LDL and HDL with respect to the duration of diabetes mellitus (p = > 0.05)

TABLE - 9

CLINICAL SIGNS OF NEUROPATHY

Duration of DM	No of patients	Peripheral Neuropathy	Autonomic Neuropathy
≤5	30	06	03
6-10	10	02	03
11-15	07	07	03
16-20	03	03	03
Total	50	18	12



This table represents the incidence of diabetic neuropathy on systemic examination with regard to duration of diabetes mellitus. Out of

50 patients,18(36%) had clinical signs of peripheral neuropathy and 12(24%) had signs of autonomic neuropathy. Of diabetes of ≤5 years duration 6 patients revealed signs of peripheral neuropathy while 3 had evidence of autonomic neuropathy. 2 patients with diabetes of duration between 6 and 10 years had signs of peripheral neuropathy while 3 had autonomic neuropathy. All the 7 patients with diabetes of duration between 11 and 15 years had signs of peripheral neuropathy while 3 had signs of autonomic neuropathy. All the 3 patients with duration of diabetes between 16 and 20 years had signs of peripheral neuropathy as well as autonomic neuropathy.

TABLE - 10

TMT RESULTS

TMT Result	Male	Female	Total
Positive	11 (27.5%)	04 (40%)	15 (35%)
Negative	29 (72.5%)	06 (60%)	35 (65%)
Total	40 (100%)	10 (100%)	50 (100%)

Table X shows the prevalence of asymptomatic coronary disease in the study population.Among 50 patients, TMT was positive in 15 (30%) and TMT was negative in 35 (70%) patients. Out of 15 positive cases 11 were males and 4 were females

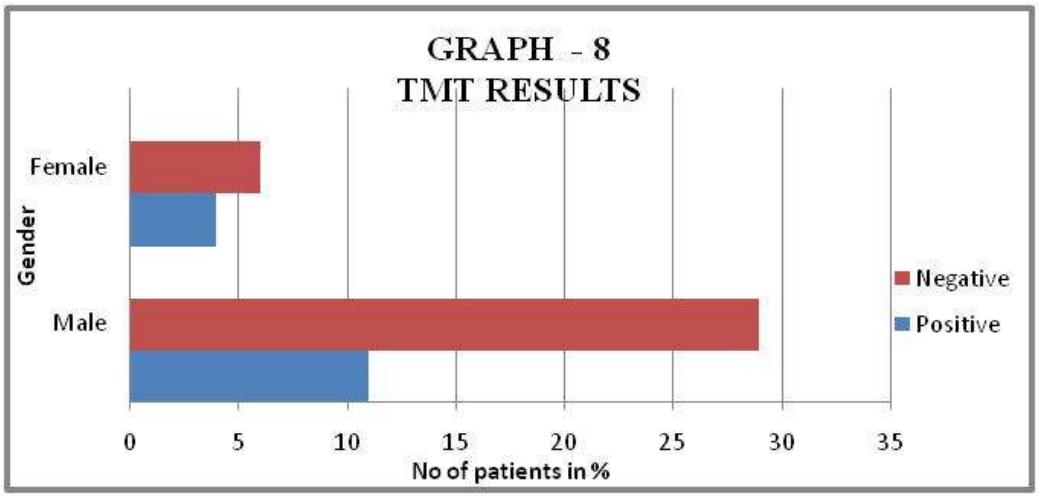


TABLE - 11

TMT RESULTS AND DURATION OF DIABETES MELLITUS

Duration of DM	TMT Positive	TMT Negative	Total
<5	05 (16.67%)	25 (83.33%)	30 (100%)
6-10	03 (30%)	07 (70%)	10 (100%)
11-15	05 (71.44%)	02 (18.56%)	07 (100%)
16-20	02 (66.67%)	01 (33.33%)	03 (100%)
Total	15 (30%)	35 (70%)	50 (50%)

This table shows the relation of asymptomatic coronary artery disease and duration of diabetes mellitus. In the present study out of 50 patients, TMT was positive in 15 (30%) and negative in 35 (70%) patients. TMT was positive in 5/30 (16.67%), 3/10 (30%), 5/7 (71.44%) and 2/3 (66.67%) patients with duration of diabetes ≤ 5, 6 to 10, 11 to 15 and 16 to 20 years respectively. This shows longer the duration of diabetes, greater the risk of asymptomatic coronary artery disease.

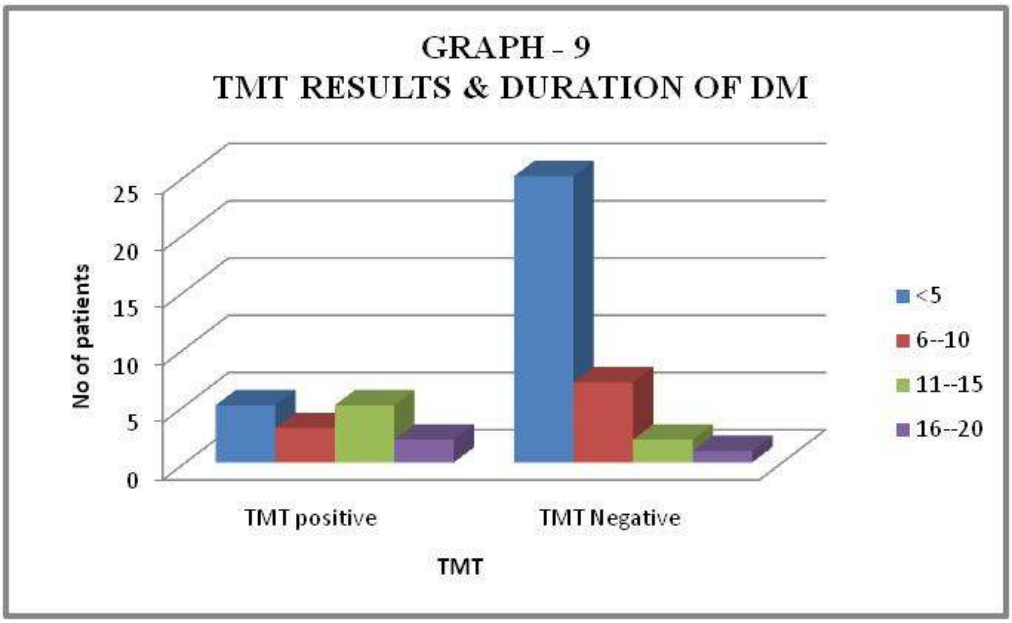


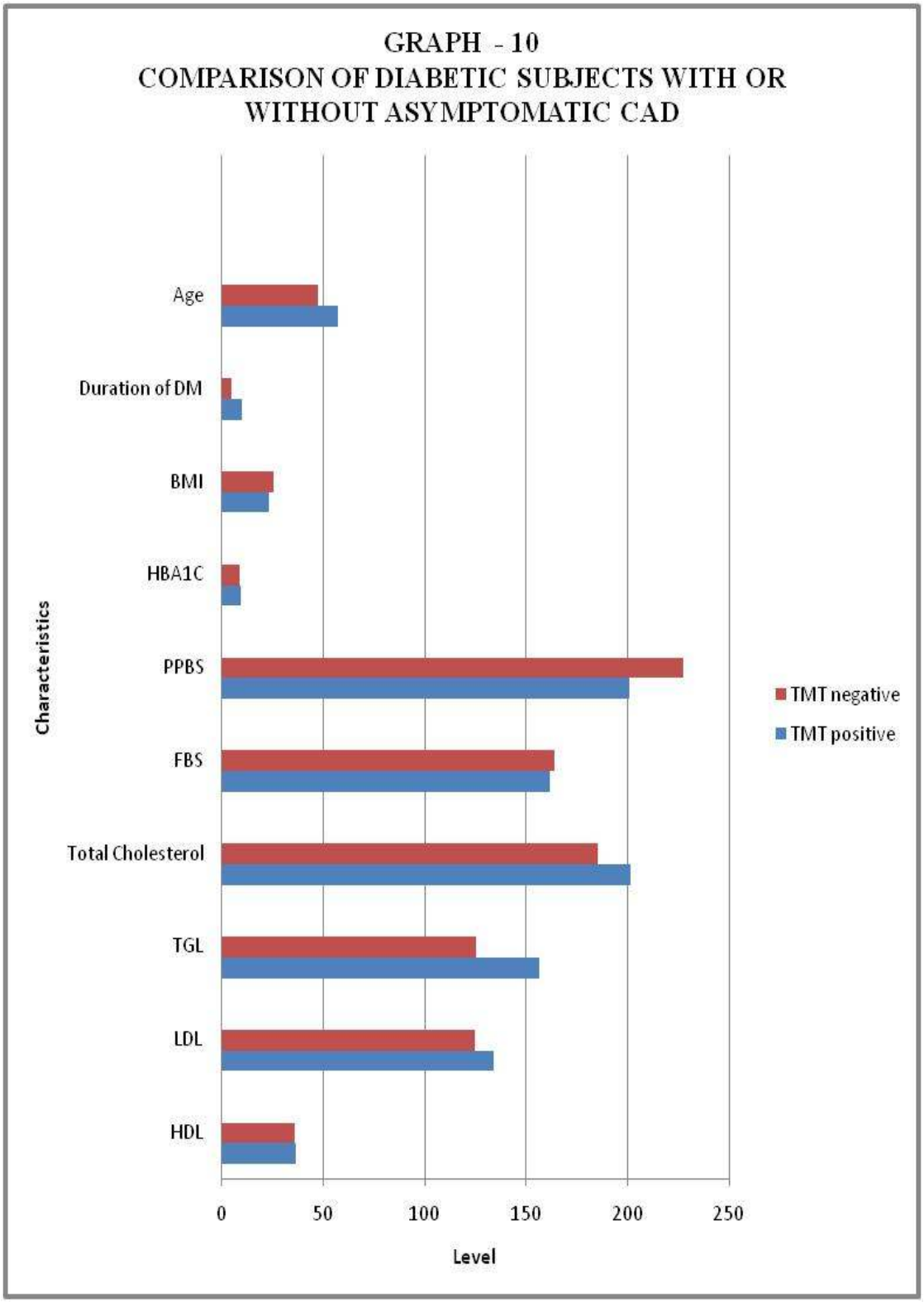
TABLE - 12

COMPARISON OF DIABETIC SUBJECTS WITH AND WITHOUT ASYMPTOMATIC CAD

Characteristics	TMT positive		TMT negative		P value	Inference
	Mean	SD	Mean	SD		
Average age	57.40	7.47	47.63	6.80	0.000	S
Av. Duration of DM	9.58	5.08	4.69	4.11	0.0026	S
Av. BMI	23.08	4.67	25.67	4.69	4.67	NS
Av. HbA1C	9.19	0.89	8.43	1.128	0.0619	NS
Av. FBS	16.160	45.30	163.71	46.18	0.87	NS
Av.PPBS	201.12	61.0	227.23	63.53	0.18	NS
Av. T. Cholesterol	201.33	32.26	185.57	32.06	0.1292	NS
Av.TGL	156.60	38.56	125.46	32.05	0.0094	S
Av. LDL	133.67	26.63	124.86	28.44	0.3127	NS
Av. HDL	36.33	3.46	35.63	3.31	0.5226	NS

GRAPH - 10

COMPARISON OF DIABETIC SUBJECTS WITH OR WITHOUT ASYMPTOMATIC CAD



The observations made with tread mill testing with reference to average age, duration of diabetes, triglyceride levels was found to have statistically significant difference in TMT positive cases and TMT negative cases. Average age in TMT positive and negative cases was 57.4 and 47.63 yrs respectively. Average duration of diabetes in TMT positive and negative cases was 9.5 and 4.69 years respectively. Average triglyceride levels in TMT positive and negative cases was 156.60and 125.46 mg% respectively.

TABLE - 13

DIABETIC PERIPHERAL NEUROPATHY AND ASYMPTOMATIC CAD

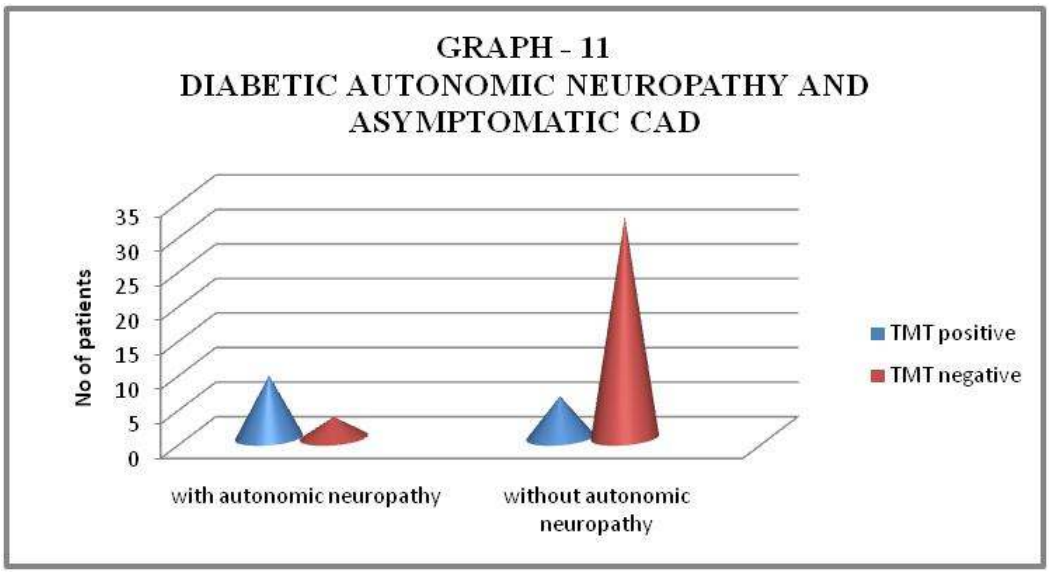
Diabetic patients	TMT result		Total n=50
	Positive(n=15)	Negative(n=35)	
With peripheral neuropathy	10	8	18
Without peripheral neuropathy	5	27	32

10 (55.55%) of the 18 diabetics with peripheral neuropathy had asymptomatic coronary artery disease while 5 (15.62%) of the 32 diabetics without peripheral neuropathy had asymptomatic coronary artery disease. This shows diabetics with peripheral neuropathy had higher incidence of asymptomatic coronary artery disease than those without it. (55.5% Vs 15.62%).

TABLE - 14

DIABETIC AUTONOMIC NEUROPATHY AND ASYMPTOMATIC CAD

Diabetic patients	TMT result		Total n=50
	Positive(n=15)	Negative(n=35)	
With autonomic neuropathy	09	03	12
Without autonomic neuropathy	06	32	38



09 (75%) out of 12 diabetics with autonomic neuropathy had asymptomatic coronary artery disease while 06 (21.95%) out of 38 diabetics without autonomic neuropathy had asymptomatic coronary artery disease. This shows diabetics with autonomic neuropathy had higher incidence of asymptomatic coronary artery disease than without it (75% Vs 21.95%).

Discussion

DISCUSSION

Coronary and peripheral vascular atherosclerosis is one of the most common and chronic complication of diabetes mellitus. A recently observed and focused aspect of coronary artery disease is its silent and asymptomatic presentation. The present study was aimed at the asymptomatic presentation of coronary artery disease in diabetes mellitus patients. It consist of two aspects; first the prevalence of asymptomatic coronary artery disease in diabetes mellitus, secondly, relation between duration of diabetes mellitus and asymptomatic coronary artery disease.

This study consisted of 50 known diabetics without clinical and ECG evidence of CAD and were evaluated for the prevalence of asymptomatic CAD by using exercise Tread mill testing. In the present study, 40 were males and 10 were females with mean age of 50.56 years ;SD of 7.59 years. Of the total, 16 patients (32%) were overweight , 5 patients (10%) were obese and remaining were with normal BMI. In our study population, more number of patients (30 i.e 60%) were having diabetes of duration equal to or less than 5 years, followed by 10 patients (20%) with the duration of 6 to 10 years, 7 patients(14%) with duration of 11 to 15 years and only 3 patients(6%) with 16 to 20 years of duration. In our 50 patients, 1(2%) was on diet control alone, 27 (54%) were on one

or the other OHA's, 12 (24%) were on one or the other form of insulin while 10 (20%) were on both oral hypoglycaemic agents and insulin. Also it was observed that patients with shorter duration of diabetes were on OHA's and patients with longer duration of diabetes were on either insulin alone or on both insulin and OHA's. Among 50 patients, TMT was positive in 15 (30%) and was negative in 35 patients (70%). Out of 15 positive, 11 were males and 4 were females. **The prevalence of asymptomatic CAD in type 2 diabetes mellitus was found to be 30%(15/50).**

Our findings were similar to previous studies. One study[18] found that 29% diabetics who were asymptomatic for coronary artery disease had silent myocardial ischaemia on 24 hour ambulatory monitoring exercise electrocardiogram. Another group[23] found 31% diabetics without prior evidence of CAD had treadmill test positive and silent myocardial ischaemia was 2.2 times more common in diabetics as compared with non diabetics.

A study[25] in India found that 38.3% of diabetics without prior coronary artery disease had silent myocardial ischaemia on exercise test. Another study[26] from India, reported 50% incidence of silent myocardial ischaemia in diabetics on exercise electrocardiogram and 35% on ambulatory monitoring. One of the study[44] concluded that the prevalence

of silent myocardial ischaemia by using exercise ECG was 17% and angiographic coronary artery disease was found in 13% of middle aged subjects with type 2 diabetes mellitus without other cardiovascular risk factors.

The other study[29] from India, found that 42.5% had evidence of silent ischemia on tread mill testing. Of these 83.7% was found to have significant CAD in coronary angiography .

So, the present study is in agreement with that diabetics have a higher prevalence of asymptomatic coronary artery disease.

Duration of type 2 diabetes mellitus and coronary artery disease

In 50 of our patients, TMT was positive in 15 patients (30%) and was negative in 35 patients (70%) .30 patients with diabetes of duration equal to or less than 5 years, TMT was positive in 5 (16.67%).10 patients with diabetes of duration between 6 to 10 years, TMT was positive in 3 (30%).7 patients with duration of diabetes between 11 and 15 years, TMT was positive in 5 (71.44%).3 patients with diabetes of duration between 16 and 20 years, TMT was found to be positive in 2 (66.67%).

Our results are similar to one study[45] who found that 70% subjects with diabetes of more than 5 years duration had associated silent myocardial ischemia while only 30% subjects with diabetes of less than 5

years duration had associated silent myocardial ischemia. Another study[31] including 500 patients with type 2 diabetes mellitus with normal resting ECG found that 12.4% patients had asymptomatic coronary artery disease on exercise treadmill testing. The abnormalities of exercise test were associated with longer duration of diabetes ($p< 0.005$).

There is paucity of data correlating the prevalence of silent myocardial ischemia with duration of diabetes. So Further studies are needed to state whether or not there is relationship between duration of diabetes and asymptomatic coronary artery disease.

Asymptomatic CAD and associated peripheral neuropathy

Peripheral neuropathy is a common microangiopathic complication of diabetes. In the present study, it was found that 55.55% (10/18) with peripheral neuropathy asymptomatic coronary artery disease while only 15.62 (5/32) without peripheral neuropathy had asymptomatic coronary artery disease. Thus, in our study diabetics with peripheral neuropathy had a greater incidence of asymptomatic coronary artery disease than those without it.(55.55% Vs 15.62%).

Our findings are in agreement with one study[17] who found that silent myocardial ischemia was associated with presence of diabetic polyneuropathy. One study[45] found that 61.5% subjects with peripheral neuropathy had silent myocardial ischemia while only 11.1% without

peripheral neuropathy had silent myocardial ischemia. However, our study is not in agreement with the one study[16], who found that there was no difference in prevalence of silent myocardial ischemia in patients with or without peripheral neuropathy. The reason for this disparity could have been due to the fact that peripheral neuropathy in their study was diagnosed by nerve conduction studies, which might have detected neuropathy at an early stages, probably at that time they did not find evidence of asymptomatic CAD disease along with peripheral neuropathy.

Asymptomatic CAD and associated autonomic neuropathy

In our study, 75% of subjects (9/12) with autonomic neuropathy had asymptomatic CAD while only 21.95% of subjects (6/38) without autonomic neuropathy had asymptomatic coronary artery disease. Thus, it was seen that, diabetics with autonomic neuropathy had higher incidence of associated asymptomatic CAD than those without it. (75% Vs 21.95%). This is in agreement with majority of studies. One group[19] found that in a diabetic population of known or suspected coronary artery disease had silent myocardial ischemia much more common with autonomic neuropathy. (92% Vs 39%). Another group[22], reported that 17% of diabetic population had silent myocardial ischemia on holtor or exercise electrocardiogram which was more common in those with

autonomic neuropathy (38% Vs 5%). In one more study[24] the incidence of asymptomatic CAD was found to be 37.5% who had evidence of autonomic neuropathy (76.9%). One study in India[25] found 38.3% to have silent myocardial ischemia with a greater prevalence in those with autonomic neuropathy (59%) than those without it(20%). Another study[46] from India found that incidence of silent myocardial ischaemia was significantly higher in patients with autonomic neuropathy. 12/13 (40%) compared to those without 3/30 (10%) .

Dyslipidemia and coronary artery disease

Lipid profile abnormalities are very common in type 2 diabetes and it has great influence on CAD. In the present study, we found average total cholesterol in TMT positive and negative cases was 201.33 mg% and 185.57 mg% respectively. Average triglyceride in TMT positive and negative cases was 156.60 mg% and 125.46 mg% respectively. Statistically significant value of p =0.0094 was found in triglyceride levels between both the groups. This was in similar with previous study[47] which found that dyslipidemia was very common in type 2 diabetics and the most common abnormality seen was increased serum triglyceride levels (73.3%) The next common abnormality was decreased serum HDL and LDL levels. Both seen in 66.7%. Coronary artery disease had a stronger correlation with high levels of triglycerides. The other study

from India[48], found that CAD had strong correlation with high levels of VLDL (0.76) triglycerides (0.82), LDL (0.23) and low HDL (- 0.81). One[49] of the studies found that frequency of hyperlipidemia in CAD was high. They found that CAD had high cholesterol levels ($p=0.04$) than those without it. The other study[29] found that cholesterol and triglyceride levels were elevated in 28 treadmill positive cases compared to 15 treadmill negative cases. ($p<0.01$).

Conclusions

CONCLUSION

1. The prevalence of asymptomatic coronary artery disease in type 2 diabetes mellitus without past history of ischemic heart disease or hypertension is 30%,

2. Longer the duration of diabetes, greater the risk of asymptomatic coronary artery disease.

3. Dyslipidemia was found to be more in diabetics who had greater prevalence of asymptomatic coronary artery disease on TMT.

4. Diabetics with clinical peripheral neuropathy and autonomic neuropathy had higher incidence of asymptomatic coronary artery disease.

5. Early screening of patients with type 2 diabetes mellitus for the evidence of asymptomatic coronary artery disease may prevent catastrophic cardiac events.

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Annexures

PROFORMA

"PREVALENCE OF ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE-2 DIABETES MELLITUS PATIENTS"

I) Patient identification data

Name : IP/OPD No :

Age : Sex :

Occupation : Address :

II) Clinical profile

History : Duration of DM :

III) Symptoms related to diabetes mellitus

Polyuria / Nocturia

Polyphagia

Polydypsia

Weight loss

Delayed wound healing

IV) Symptoms suggestive of microvascular complications Nephropathy

Puffiness of face / swelling of feet

Oliguria / anuria

Recurrent UTI

Retinopathy

Visual loss – Total / Partial

Blurring of vision

Peripheral neuropathy

Numbness

Parasthesias

Pain

Proximal muscle weakness

Autonomic neuropathy

Presyncope / syncope

Palpitations

Gustatory sweating

Anhydrosis

Nocturnal diarrhea / faecal incontinence

Urinary incontinence

Impotence

Treatment history

Diet alone

Oral hypoglyacemic agents

Insulin

OHA + Insulin

Family history

DM/HTN/IHD

Personal history

Diet

Habits

Menstrual history

Oral contraceptives

General physical examination

Weight in kgs

Height in mtr. BMI

Hip Waist circumference

Face: puffiness

Eyes Fundus

Pallor

Pigmentation

Odema

Deep vein thrombosis

Vital signs

Pulse

Blood pressure - Supine and Standing

Systemic examination

Respiratory system

Cardiovascular system

Per abdomen

Central nervous system

Investigative profile

A) Hematological

Hemoglobin

TLC/DLC

B) Biochemical

Fasting blood sugar

Post prandial blood sugar

Fasting lipid profile

Cholestrol

Triglyceride

HDL

LDL

Urea

S. Creatinine

HbA1C

C) Urine examination

Routine and microscopic examination

Microalbuminuria

D) X-ray chest (PA) view:

E) Electrocardiogram

F) Treadmill test

S No	Age	Sex	IP No.	Duration of DM	symptoms of DM	P neuropathy symptoms	Autonomic N symptoms	Treatment history	Family history	BMI	Pulse	SBP	DBP	CVS	P Neuropathy	A Neuropathy	HbA1C	FBS	PPBS	T Cholesterol	TGL	HDL	LDL	Urea	Creatinine	Urine albumin	CXR	TMT
1	54	M	61223	3	_	-	-	O	+	21.8	70	132	80	N	+	-	9.5	233	358	200	150	32	90	26	1.1	-	N	+
2	51	M	1556	2	_	-	-	O	+	26.6	80	130	90	N	_	-	8.4	168	215	150	140	38	84	24	0.8	-	N	_
3	63	F	43371	19	+	+	+	I	-	38	86	140	90	N	_	+	9.4	291	336	240	200	30	134	40	0.8	-	N	+
4	46	M	3987	9	_	+	-	O	+	20.2	84	136	90	N	+	+	7.7	145	170	173	120	32	117	34	0.8	-	N	_
5	56	M	4902	2	_	-	-	O	+	24.4	78	140	90	N	_	-	8	180	260	150	120	40	86	32	1.4	-	N	_
6	49	M	27746	3	_	-	-	O	+	27.3	76	120	90	N	+	-	7.7	160	190	173	100	40	113	30	0.7	-	N	+
7	58	F	8453	15	_	+	-	I	+	26.9	80	130	80	N	+	-	8.6	154	206	234	180	40	158	36	0.9	-	N	-
8	33	F	23749	2	_	-	-	OI	+	23.1	70	140	90	N	-	-	9.4	168	204	225	190	40	147	22	0.8	-	N	-
9	62	M	8442	7	_	-	-	O	-	20.4	78	136	80	N	-	-	7.2	125	170	170	130	40	104	36	0.9	-	N	-
10	58	M	28394	4	_	-	-	O	+	19.4	78	140	90	N	-	+	11.6	136	204	160	90	32	110	22	0.5	-	N	+
11	34	M	7453	12	_	+	-	I	+	20.5	74	130	70	N	+	+	10.5	158	324	173	140	40	105	30	0.7	-	N	-
12	52	M	29839	4	_	-	-	O	+	24.6	80	120	80	N	_	_	8.5	146	216	180	100	34	126	20	0.9	-	N	-
13	44	M	3244	14	_	+	+	I	-	21.2	86	124	70	N	+	+	7.7	175	178	174	80	32	126	30	0.4	-	N	-
14	65	M	678	17	+	+	-	I	-	26.2	84	126	80	N	+	+	7.4	233	168	200	100	32	100	26	0.9	-	N	-
15	58	M	14789	1	+	-	-	D	+	26.9	90	140	80	N	+	-	7.6	136	180	133	128	32	75	28	0.8	-	N	+
16	56	M	9744	5	_	-	-	OI	+	27.3	84	146	90	N	-	-	7.8	148	186	212	188	30	139	22	0.6	-	N	-
17	48	M	4778	3	_	-	-	O	-	22.5	86	130	80	N	-	-	7.4	154	176	150	80	34	100	24	0.7	-	N	-
18	54	F	23747	4	_	-	-	O	+	20.4	96	140	80	N	-	-	7.6	128	190	152	82	34	102	30	0.5	-	N	+
19	38	M	8887	8	_	-	-	OI	-	19.4	76	130	80	N	-	-	7.4	148	204	207	154	36	140	34	0.5	-	N	-
20	67	M	9432	3	+	-	+	O	+	19.6	78	130	80	N	+	-	7.2	152	216	164	140	38	98	32	0.6	-	N	-
21	68	M	7920	9	+	+	+	O	+	27.3	72	124	80	N	+	+	11.2	204	358	173	100	40	113	38	0.6	-	N	+
22	56	F	67889	2	_	_	-	O	-	28.2	68	126	70	N	_	-	8.9	190	186	234	210	30	165	32	0.9	-	N	+
23	46	M	2847	13	_	+	-	I	-	26.8	70	128	80	N	+	-	7.9	176	176	225	160	36	110	28	0.9	-	N	-
24	53	M	71234	5	_	-	-	OI	+	32.1	68	114	70	N	-	-	8.8	186	190	240	250	34	152	26	0.8	-	N	-
25	55	M	63821	3	_	-	-	O	-	23.4	72	120	80	N	-	-	8.8	175	170	174	174	32	90	30	0.4	-	N	-

S No	Age	Sex	IP No	Duration of DM	symptoms of DM	P neuropathy symptoms	Autonomic N symptoms	Treatment history	Family history	BMI	Pulse	SBP	DBP	CVS	P Neuropathy	A Neuropathy	HbA1C	FBS	PPBS	T Cholesterol	TGL	HDL	LDL	Urea	Creatinine	Urine albumin	CXR	TMT
27	57	M	7364	15	+	+	-	I	+	26.3	84	130	70	N	+	+	7.9	136	190	133	140	34	134	28	0.8	-	N	+
28	44	M	7942	10	-	+	-	O	+	25.5	86	136	90	N	+	-	8.8	148	206	212	136	34	117	22	0.8	-	N	-
30	51	M	66879	2	-	-	-	O	+	23.4	80	128	80	N	-	-	8.6	128	210	200	164	40	113	30	0.4	-	N	-
31	55	M	56726	2	-	-	-	O	+	34.2	86	120	70	N	-	-	9.4	186	178	286	204	30	146	34	0.9	-	N	-
32	49	M	1388	12	-	+	-	O	+	20.7	84	136	80	N	-	-	7.2	136	180	170	120	40	96	32	0.8	-	N	+
33	42	M	3744	8	-	-	-	O	-	23.4	72	128	70	N	-	-	11.6	240	324	164	110	32	112	38	0.6	-	N	_
34	48	F	8893	4	+	-	-	OI	+	23.8	88	126	70	N	+	+	7.9	136	158	150	96	40	56	22	0.7	-	N	+
35	35	M	29848	5	+	-	+	OI	+	32	68	130	80	N	+	-	8.8	236	360	240	199	34	156	24	0.5	-	N	+
36	56	M	14589	4	_	-	_	O	-	22	68	118	70	N	_	-	7.4	158	196	144	100	32	86	30	0.5	-	N	_
37	57	M	546	16	+	+	+	I	-	24.6	72	130	80	N	+	+	7.6	146	204	178	112	40	104	20	0.6	-	N	+
38	45	F	46821	7	-	-	-	O	+	21.4	76	120	80	N	-	-	7.4	175	210	150	126	40	90	30	0.9	-	N	-
39	64	M	9848	9	-	-	-	I	+	23	84	130	80	N	-	-	7.6	138	178	133	158	40	88	26	0.8	-	N	-
40	58	M	26366	3	-	-	-	OI	+	23.3	86	140	90	N	-	-	8.4	291	180	170	134	40	114	28	0.6	-	N	+
41	44	M	36767	2	-	-	-	O	-	20.5	74	136	80	N	-	-	8.2	185	206	165	122	40	94	40	0.7	-	N	_
42	47	F	8484	9	+	+	-	I	+	21.2	78	140	80	N	+	-	7.8	180	188	158	146	32	108	34	0.6	-	N	+
43	58	M	7598	7	_	-	-	I	+	28.1	76	130	80	N	_	-	7.2	204	180	210	206	30	142	32	0.7	-	N	-
44	54	M	64622	3	+	+	-	O	+	27.2	80	120	70	N	+	+	9.4	235	310	214	214	34	129	30	0.5	-	N	-
45	41	M	8764	9	-	-	-	I	-	23.7	70	124	70	N	-	+	8.6	176	196	188	136	32	98	36	0.5	-	N	-
46	46	M	9576	5	-	-	-	OI	+	34.2	78	136	80	N	-	-	7.4	142	170	234	218	32	138	30	0.6	-	N	-
47	47	M	46587	4	-	-	-	O	-	26.3	86	132	80	N	-	-	7.6	146	168	155	100	34	92	26	0.6	-	N	-
48	42	M	5788	6	-	-	-	O	+	23.8	74	120	70	N	-	-	7.5	140	184	167	98	40	88	28	0.9	-	N	-
49	48	M	23774	5	-	-	-	OI	+	23.2	80	132	80	N	-	-	8	168	198	174	112	38	76	40	0.8	-	N	-
50	37	M	36246	2	-	-	-	O	+	22	76	136	80	N	-	-	8.2	246	310	246	186	38	64	34	0.8	-	N	-

CONSENT FORM

Yourself Mr/Mrs/Ms _____ are being asked to be a participant in the study titled – "To study the prevalence of Asymptomatic Coronary Artery Disease in type 2 Diabetes Mellitus" in CMC Hospital Conducted by Dr. Suja P Sukumar, Post Graduate student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into inclusion criteria. You can ask any questions you may have before agreeing to participate.

Purpose of the research

1. To study the prevalence of asymptomatic CAD in type 2 diabetes mellitus.
2. To study the relation of asymptomatic CAD with duration of diabetes mellitus.

Procedures involved

This research is intended to study type 2 diabetes mellitus patients without clinical and ECG evidence of ischemic heart disease to perform treadmill test using Bruce Protocol for the presence of asymptomatic CAD.

Decline from participation

You have the option to decline from participation in the study without any discrimination and you will be treated as per the existing protocol for your condition.

Privacy and confidentiality

Privacy of individual will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization publish results

Results of the study may be published for scientific purposes and / or presented to scientific groups; however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me and I may ask questions at any time.

_____ _____

Signature of Left Hand thumb Impression (Volunteer Subject) Date

_____ _____

Signature (Witness) Date

ABBREVIATIONS

AGE	-	Advanced glycated end products
BMI	-	Body mass index
CABG	-	Coronary Artery Bypass Grafting
CAD	-	Coronary Artery Disease
ECG	-	Electro cardiography
ESRD	-	End stage renal disease
FPG	-	Fasting plasma glucose
GDM	-	Gestational Diabetes Mellitus
HbA1C/A1C	-	Glycosylated hemoglobin
HDL	-	High density lipoprotein
TGL	-	Triglyceride
LDL	-	Low density lipoprotein
LP(a)	-	Lipoprotein a
IDL	-	Intermediate density lipoprotein
IFG	-	Impaired Fasting glucose
IGT	-	Impaired Glucose tolerance
LBBB	-	Left Bundle branch block
LVH	-	Left Ventricle hypertrophy
MI	-	Myocardial infarction
NAD	-	Nicotinamide Adenosine Diphosphate
NADH	-	Nicotinamide adenosine Diphosphate Hydrogenase
NPDR	-	Non Proliferative Diabetic Retinopathy
OGTT	-	Oral glucose tolerance test

PDR	-	Proliferative Diabetic Retinopathy
THR	-	Target Heart Rate
SBP	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
OHA	-	Oral Hypoglycemic Agent
TMT	-	Treadmill test
VLDL	-	Very low density lipoprotein